Drug Class Review

Atypical Antipsychotic Drugs

Final Update 3 Report
Evidence Tables

July 2010

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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Abbreviations used in evidence tables

Abbreviation	Meaning
AAP	Atypical Antipsychotic
ABC	Aberrant Behavior Checklist
ACT	Active-control trial
AD	Alzheimer's Disease
ADHD	Attention deficit hyperactive disorder
ADI-R	Autism Diagnostic Interview-Revised
AE	Adverse event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
AMDP-5	Association for Methodology and Documentation in Psychiatry adverse event questionnaire
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ASD	Autism spectrum disorders
ASEX	Arizona Sexual Experience Scale
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BAS	Behavioral Approach System scale
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease
bid	Twice daily
BIS	Behavioral Inhibition System scale
BMI	Body mass index
BNT	Boston Naming Test
BPAD	Empirical Behavioral Pathology in Alzheimer's Disease scale
BPRS	Brief Psychiatric Rating Scale
BRMS	Bech Rafaelsen Melancholia Scale
BWISE	Body weight, image and self-esteem evaluation questionnaire
CBCL	Child Behavior Checklist
CCT	Controlled clinical trial
CDI	Children's Depression Inventory scale
CDSS	Calgary Depression Scale for Schizophrenia
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CGI	Clinical global impressions (S, C and I versions)
CGI-I	Clinical global impression scale - Improvement
CGI-S	Clinical global impression scale - Severity
CI	Confidence interval
CMAI	Cohen-Mansfield Agitation Inventory
CMMSE	Cantonese version of Mini-Mental State Examination
CNS	Central nervous system
COGLAB	COGnitive LABoratory (computer-assisted cognitive test battery)
COPD	Chronic obstructive pulminary disease
COSTART	US FDA Coding Symbols for a Thesaurus of Adverse Reaction Terms
CPM	Concomitant psychotropic medication
CPRS	Conners Parent Rating Scale
CPT	Continuous Performance Test
CR	Controlled release

Abbreviation	Meaning
CSFQ	Changes in Sexual Functioning Questionnaire
CSQ-8	Client Satisfaction Questionnaire-8
CTD	Cognitive Test for Delirium
CUAD	Chemical Use, Abuse, and Dependence Scale
CV	Cardiovascular
CVA	Cerebrovascular accident
CVLT	California Verbal Learning Test
CVS	Cardiovascular system
d	Day
DAI	Drug Attitude Inventory
DAS	Disability Assessment Schedule
DB	Double-blind
DIEPSS	Drug-induced Extrapyramidal Symptom Scale
DIS III	Diagnostic Interview Schedule III
DISCUS	Dyskinesia Identification System Condensed User Scale
dL	Deciliter
DOTES	Dosage Record and Treatment Emergent Symptom Scale
DSDT	digit span distraction test
DSM-III	Diagnostic and Statistical Manual of Mental Disorders-Third Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition
DVP	Digital volume pulse
E-BEHAVE-ED	Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale
ECG	Electrocardiogram
ECT	Electroconvulsive therapy
EEG	Electroencephalogram
EF	Ejection fraction
EPS	Extrapyramidal symptoms
ER	Extended release
ESRS	Extrapyramidal Symptom Rating Score
FAST	Functional Assessment Staging Rating Scale
FDA	US Food and Drug Administration
FGIR	Final Global Improvement Rating
FU	Follow-up
g	Gram
GAF	Global Assessment of Functioning Scale
GAS score	Global Assessment Scale Score
GBAS	General Behavior Assessment Scale
GI	Gastrointestinal
GP	General practitioner
GPS	General Psychopathology Subscale
h	Hour
HAM-D	Hamilton Depression Scale
HAS	Hamilton Anxiety Scale
HDI	Hamilton Depression Inventory
HDL-C	High density lipoprotein cholesterol
HMO	Health maintenance organization
HOMA	Homoeostasis model assessment index

Abbreviation	Meaning
HPL	Hyperprolactinemia
HR	Hazard ratio
HRQOL	Health related quality-of-life
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
IDS-C	Inventory of Depressive Symptomatology-Clinician Rated
INS	Insulin
IR	Immediate release
IRI	Insulin resistance index
ISST	Information-Seeking Skills Test
ITT	Intention-to-treat
L	Liter
LA	Long acting
LDL-C	Low-density lipoprotein cholesterol
LFT	Liver function test
Li	Lithium
LOCF	Last Observation Carried Forward
LQL	Lehman Quality of Life
LS means	Least squares means
MADRS	Montgomery-Asberg Depression Rating Scale
MANCOVA	Multivariate analysis of covariance
MASC	Multidimensional Anxiety Scale for Children
mcg	Microgram
MDB	Movement Disorder Burden
MDD	Major depressive disorder
MDE	Major depressive episode
mg	Milligram
min	Minute
MINI	Mini International Neuropsychiatric Interview
MITT	Mother-Infant Treatment Team
mL	Milliliter
MLDL	Munich List of Quality-of-Life Dimensions
MMSE	Mini-Mental State Examination
mo	Month
MOSES	Multidimensional Observational Scale for Elderly Subjects
MSQ	Medication Satisfaction Questionnaire
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NAART-R	North American Adult Reading Test-Revised
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NIP	National Institute of Psychiatry
NMS	Neuroleptic malignant syndrome
NOSGER	Nurses' Observation Scale for Geriatric Patients
NOSIE	Nurses' Observation Scale for Inpatient Evaluation

Abbreviation	Meaning
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory-Nursing Home
NR	Not reported
NRS	Neurologic Rating Scale
NS	Not significant
NSA	Negative Symptom Assessment
NSD	No significant difference
OAS	Overt Aggression Scale
OAS-M	Modified Overt Aggression Scale
OR	Odds ratio
P	*P* value
P	Placebo
PANSS	Positive and Negative Syndrome Scale
PANSS-D	PANSS Depression Cluster
PANSS-EC	Positive and Negative Syndrome Scale-Excited Component
PCT	Placebo-controlled trial
PDD	Pervasive developmental disorder
PDD-NOS	Pervasive developmental disorder - not otherwise specified
PDS	Progressive Deterioration Scale
PEAT	Penn Emotional Acuity Test
PETiT	Personal Evaluation of Transitions in Treatment
PGDRS	Psychogeriatric Dependency Rating Scale
PGWB	Psychological General Well-Being
PPR	Positive Psychopathology Rating
PPY	Per person year
PRAEQ	Prolactin Related Adverse Event Questionnaire
PSP scale	Personal and Social Performance scale
PSQI	Pittsburgh Sleep Quality Index
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
qd	Once daily
QLDS	Quality-of-Life in Depression Scale
QLI	Lehman Brief Quality-of-Life Interview
QOL	Quality-of-life
QUALID	Quality-of-Life in Late-Stage Dementia scale
RAAP	Rating of Aggression Against People and/or Property Scale
RAVLT	Rey Auditory Verbal Learning Task
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomized controlled trial
RDQ	Reflux Disease Questionnaire
RFS	Role Functioning Scale
RODOS-UK	UK Risperidone Olanzapine Drug Outcomes Studies in Schizophrenia Program
RR	Relative risk
SADS-CB	Schedule for Affective Disorders and Schizophrenia-Change Bipolar Scale
SAFE	Social Adaptive Functioning Evaluation
SAGE	Systematic Assessment of Geriatric drug use via Epidemiology
SANS	Scale for Assessment of Negative Symptoms
SAPS	Scale for the Assessment of Positive Symptoms

Abbreviation	Meaning
SAR-S	Simpson Angus Rating Scale for Extrapyramidal Side Effects
SAS	Social Adjustment Scale
SB	Single-blind
SCID	Structural Clinical Interview for DSM-IV
SD	Standard deviation
SE	Standard error
SFS	Social Functioning Scale
SIP	Sickness Impact Profile
SMB	Suicide Monitoring Board
SOFA	Social and Occupational Functioning Assessment
SOT	Standard olanzapine tablets
SR	Sustained release
SSPA	Social Skills Performance Assessment
SSRI	Selective serotonin reuptake inhibitor
SSTICS	Subjective Scale to Investigate Cognition in Schizophrenia
SUD	Substance use disorder
SVLT	Serial Verbal Learning Test
SWMT	Spatial Working Memory Test
SWN	Subjective Well-being under Neuroleptic Treatment Scale
SWS	Slow-wave sleep
TA	Typical Antipsychotic drugs (e.g. haloperidol, perphenazine)
TAS	Total Aggression Severity
TC	Total cholesterol
TD	Tardive dyskinesia
TEAEs	Treatment emergent adverse events
TESS	Treatment Emergent Symptom Scale
tid	Three times daily
TMT	Trail Making Test
TNR	Treatment nonresponsive
ToL test	Tower of London test
UKU-SERS	Udvalg for Kliniske Undersogelser Side Effect Rating Scale
VAS	Visual analog scale
vs.	Compared with (versus)
WAIS-R	Wechsler Adult Intelligence Scale - Revised
WCST	Wisconsin Card Sorting Test
WD	Withdrawal
WHO	World Health Organization
WHO-QL	World Health Organization - Quality-of-Life
WHR	Waist-hip circumference ratio
WISC-R	Wechsler Intelligence Scales for Children - Revised
WMS-R	Wechsler Memory Scale - Revised
XR	Extended release
y	Year
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YMRS	Young Mania Rating Scale

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Addington, 2004 DB, RCT, parallel Addington 2009	schizophrenia, schizoaffective disorder, 18-65 years of age, PANSS total score ≥60, a score of ≥4 on 2 of the PANSS core items.	ziprasidone 40-80 mg BID. (N=149) or risperidone 3-5mg BID. (N=147) 8 weeks duration	>3 days washout of anti-psychotics, anticholinergic agents, beta-blockers	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Addington, 2004 DB, RCT, parallel Addington 2009	Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity of Illness Scale (CGI-S), CGI-Improvement scale (CGI-I), Brief Psychiatric Rating Scale (BPRSd), Movement Disorder Burden (MDB), Global Assessment of Functioning (GAF), Montgomery-Asberg Depression Rating Scale (MADRS), UKU Side Effect Rating Scale, Simpson-Angus Rating Scale, Barnes Akathisia Scale, Abnormal Involuntary Movement Scale (AIMS), Movement Disorder Burden (MDB), laboratory data, vital signs, body weight, ECG	Mean age: 35 years 72.5% Male Ethnicity NR	NR	NR/NR/296

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Addington, 2004 DB, RCT, parallel Addington 2009	NR/NR/198	Efficacy evaluations: LS mean change from baseline to last visit: PANSS total: Z: -25.8 vs R: -27.3 CGI-S: Z: -1.1 vs R: -1.2 PANSS negative subscale: Z: -6.4 vs R: -6.4 BPRSd total: Z: -15.2 vs R: -15.9 BPRSd core: Z: -5.5 vs R: -6.0 GAF: Z: 16.5 vs R: 15.6 Body weight increase (>7% change): Z: 10(8.2%) vs R: 20(16.0%) Body weight decrease (>7% change): Z: 9(7.4%) vs R: 3(2.4%) Long term data from 44 weeks extension study (Addington 2009) Z vs R Mean change from baseline in PANSS total Change(SE) -28.0 (3.8) vs -33.2 (3.3), p=0.29 Mean change from baseline in CGI-S (SE) -1.2 (0.2) vs -1.6 (0.2), p=0.22 Mean change from baseline in GAF (SE) 14.4 (3.0) vs -19.1 (3.6),p=0.22 Mean change from baseline in MADRS total score -5.2 (1.3) vs -4.3 (1.2), p=0.63

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Addington, 2004 DB, RCT, parallel Addington 2009	Patient self-report, laboratory tests, Sexual dysfunction questionnaire	Treatment-emergent adverse events reported: Z: 113 (75.8%) vs R: 122(83.0%) Events reported by patients: Insomnia: Z: 37(24.8%) vs R: 18(12.2%) Somnolence: Z: 31(20.8%) vs R: 26(17.7%) Agitation: Z: 24(16.1%) vs R: 20(13.6%) Headache: Z: 23(15.4%) vs R: 27(18.4%) Akathisia: Z: 19(12.8%) vs R: 30(20.4%) Tremor: Z: 15(10.1%) vs R: 14(9.5%) Sexual Dysfunction Questionnaire: Symptom absent at baseline and present at last visit: Erectile dysfunction: Z: 8% vs R: 10% Ejaculatory dysfunction: Z: 3% vs R: 11% Increased libido: Males: Z: 1% vs R: 5% Females: Z: 10% vs R: 0% Decreased libido: Males: Z: 9% vs R: 15% Females: Z: 5% vs R: 3% Orgastic dysfunction: Males: Z: 5% vs R: 13% Females: Z: 0% vs R: 0% Adverse events reported in the 44 weeks continuation study (Addigton 2009) occurring in >10% of patients Z vs R Agitation:16.1% vs 16.9%, Akathisia: 27.4% vs 28.6%, Anxiety: 16.1% vs 11.7%, Constipation: 6.5% vs 11.7%, Dizziness: 11.3% vs 7.8%, Headache: 21.0% vs 23.4%, Hypertonia: 3.2% vs 11.7%, Insomnia: 32.3% vs 18.2%, Nausea: 14.5% vs 9.1%, Respiratory tract infection: 8.1 vs 15.6%, Somnolence: 24.2 vs 28.6%, Tremor: 11.3% vs 13.0%, vomiting: 12.9 vs 3.9%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Addington, 2004 DB, RCT, parallel Addington 2009	Simpson-Angus scores: Z: -0.57 (0.33) vs R: -0.23 (0.33); P=.04 Barnes Akathisia scores: Z: -0.28 vs R: +0.28 (0.21); P=.04 AIMS scores: Z: -0.04 (0.17) vs R: -0.25 (0.17); P=.3 MDB scores: Z: 0.20 vs R: 0.35; P=.015 Number of patients who experienced a movement disorder adverse event: R: 54(36.7%) vs Z: 44(29.5%) % of patients with Extrapyramidal reaction in 44 week continuation study (Addington 2009) Z vs O: 12.9% vs 9.1%	98 withdrawals; 18 withdrawals due to adverse events	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Akerele, 2007 RCT	Met DSM-IV criteria for schizophrenia or schizoaffective disorder; met DSM-IV criteria for current cocaine and/or marijuana abuse or dependence; and were using marijuana at least twice/week, or cocaine at least once/week on average during 3 months prior to study enrollment Exclusion criteria: pregnant; currently psychologically dependent on alcohol or other drugs such that they had significant withdrawal symptoms in the past (except nicotine and caffeine); unstable psychiatric symptomatology; unstable medical condition; enzyme function tests > 3 times upper limit of normal; history of seizures or neuroleptic malignant syndrome; commission of violent crime in past 2 years; not responded to olanzapine or risperidone in past; or score > 30 on positive and negative sub-scales of Positive and Negative Symptom Scale	olanzapine: 5-20 mg/day risperidone: 3-9 mg/day duration: 14 weeks	2 week cross-taper phase	NR
Alvarez, 2006 RCT, open-label Outpatients	DSM-IV schizophrenia diagnosis; baseline summary SANS score ≥10; age 18-65 yrs; if previously treated with antipsychotics, only those patients treated with first generation drugs accepted; no psychiatric hospitalizations within 3 months of study entry	olanzapine 10 mg/day* risperidone 3 mg/day* *recommended starting doses; titration allowed at investigator's discretion mean doses during time on trial: olanzapine 12.2 mg/day (SD 5.8) risperidone 4.9 mg/day (SD 2) end point mean doses: olanzapine 13.1 mg/day (SD 6.9; median 10 mg/day) risperidone 5.1 mg/day (SD 2.3; median 6 mg/day)	None; overlapping of medications allowed during the first month of study participation	biperiden; benzodiazepines up to 40 mg/day diazepam equivalent

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Akerele, 2007 RCT	Marijuana Craving Report, Cocaine Craving Report (each of the 3 weekly visits), Quantitative Substance Use Inventory (weekly), PANSS (biweekly), HAM-D (monthly), CGI (weekly), AIMS (weekly)	Mean age: 35.5 yrs Male: 89% African American: 54% Hispanic: 32% Caucasian: 14%	Current marijuana use: 93% Current cocaine use: 78.6%	76/29/28
Alvarez, 2006 RCT, open-label Outpatients	SANS summary score assessed at wks 8, 24 and 48 (or at early withdrawal) Monthly assessments wks 1-24; every other month weeks 25-48	Mean age: 36.3 yrs 72% male Ethnicity NR	Schizophrenia type: paranoid 64%; residual 19%; undifferentiated 13%; disorganized 3%; catatonic <1% Mean SANS summary score: 14.3 Mean CGI: 4.4 Mean Calgary Depression Score: 4.2 Statistically significant difference between intervention groups for mean baseline weight (O 73.8 kg v R 80.5 kg; P=0.0005) and mean baseline BMI (O 25.9 v R 27.5; P=0.0072)	NR/NR/250

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Akerele, 2007 RCT	12 dropped out/16 completed	Marijuana use: Urine toxicology showed significant decrease in both groups (Z= -2.52, *P*=0.01) Self-reported marijuana craving showed significant x time interaction (Z=2.06, *P*=0.04) for risperidone group; virtually no change in craving severity for olanzapine group Cocaine use: No significant differences in terms of cocaine craving over time Self-reported drug use: Olanzapine group reported on avg. significantly fewer days of use than risperidone group (3 days vs. 4.3 days; Z= -2.27, *P*=0.02) PANSS positive and negative subscales: Severity decreased over time on positive subscale for both groups (Z= -2.53, *P*=0.01) but no significant between-group differences (Z= 0.49, *P*=0.62) Severity did not decrease significantly over time for negative subscale (Z=0.34, *P*=0.73) HAM-D Mean scores at study end were approximately 7 points for both groups; no significant difference between groups in mean change from baseline (olanzapine 0.14 [0.91], risperidone 0.03 [0.70]; t=.031, df=20, P=0.76) AIMS Worsening of abnormal movements: olanzapine=0, risperidone=1 Improvement of abnormal movements: olanzapine=3, risperidone=4
Alvarez, 2006 RCT, open-label Outpatients	87/12/235 efficacy; 247 safety	SANS summary score, mean change from baseline: O -6.0 v R -4.7; P=0.0151; effect size 0.34 Affective flattening, mean change from baseline: O -9.1 v R -6.5; P=0.0065; effect size 0.39 Speech difficulty, mean change from baseline: O -5.2 v R -4.2; P=0.0747; effect size 0.22 Avolition/apathy, mean change from baseline: O -4.7 v R -3.5; P=0.0283; effect size 0.03 Anhedonia/unsociability, mean change from baseline: O -4.8 v R -3.5; P=0.1216; effect size 0.26 Attention, mean change from baseline: O -3.6 v R -2.6; P=0.1106; effect size 0.34 SANS composite, mean change from baseline: O -27.4 v R -20.4; P=0.0183; effect size 0.35 SAPS summary score and SAPS composite score changes favored olanzapine (P=0.0207 and P=0.0115 respectively) CGI score significantly favored olanzapine (P=0.0082) No SS difference in Calgary Depression Score (P=0.9745)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Akerele, 2007 RCT	Simpson-Angus Scale, and weekly psychiatrist assessments	Sedation: olanzapine 54%, risperidone 77% No withdrawals in either group due to AEs
Alvarez, 2006 RCT, open-label Outpatients	EPS assessed at each visit using the EPS questionnaire from the UKU Scale; physiological changes (i.e. weight gain) recorded at each visit	Percentage of pts experiencing any AE: O 62.9% (n=78) v R 72.4% (n=89); P=NS Mean weight gain: O 3.8 kg (SD 6.1) v R 2.1 kg (SD 6.0) Proportion of pts with weight increase >7%: O 40.7% (n=35) v R 17.3% (n=13); P=0.0012 Specific AEs: O v R Anxiety: 12.1% (n=15) v 13.8% (n=17); P=0.6866 Insomnia: 6.5% (n=8) v 13.8% (n=17); P=0.0549 Tremor: 5.6% (n=7) v 13.8% (n=17); P=0.0301 Libido decrease: 5.6% (n=7) v 6.5% (n=8); P=0.7775 Akathisia: 1.6% (n=2) v 8.9% (n=11); P=0.0099 Somnolence: 4.0% (n=5) v 6.5% (n=8); P=0.3844 Headache: 5.6% (n=7) v 4.1% (n=5); P=0.5636 Weight increase: 6.5% (n=8) v 2.4% (n=3); P=0.1264 Hypertension: 5.6% (n=7) v 3.3% (n=4); P=0.3620 Appetite increased: 6.5% (n=8) v 1.6% (n=2); P=0.1023 Muscle rigidity: 1.6% (n=2) v 6.5% (n=8); P=0.596 Sexual dysfunction: 0.8% (n=1) v 5.7% (n=7); P=0.0357

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Akerele, 2007 RCT	NR	12 total withdrawals 0 due to adverse events	
Alvarez, 2006 RCT, open-label Outpatients	Treatment emergent and worsening of pre-existing EPS based on UKU questionnaire affected 28.9% (n=35) of olanzapine and 50.4% (n=61) of risperidone patients (P=0.0006) Specific symptoms: Rigidity: O 5% (n=6) v R 25.6% (n=31); p<0.001 Hypokinesia/akinesia: O 10.7% (n=13) v R 24.0% (n=29); P=0.0103 Akathisia: O 7.4% (n=9) v R 18.2% (n=22); P=0.0198	72 total withdrawals 10 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
AstraZeneca D1441C00112 DB RCT International (43 sites)	Inclusion: Male and female inpatient and outpatient adolescents (aged 13 to 17 years), with a DSM-IV diagnosis of schizophrenia as confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime Version were recruited for the study; PANSS total score of ≥60 and a score of 4 or greater on delusions (P1), conceptual disorganization, (P2), or hallucinations (P3) at both screening and randomization.	Quetiapine 400 mg/day vs Quetiapine 800 mg/day or placebo given in divided doses either bid or tid 6 weeks	medication washout period of 1 to 28 days	NR
AstraZeneca, Data on File, Study D1444C00132 DB RCT	Acutely ill male and female patients, 18 to 65 years of age, diagnosed with schizophrenia as stated in DSM-IV; PANSS total score of at least 70 and a CGI Severity of Illness score of at least 4 at randomization	Quetiapine SR 400 mg/day, 600 mg/day and 800 mg/day, quetiapine IR 400 mg/day and placebo 6 weeks	Not reported (DB phase following an enrollment period of up to 7 days)	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
AstraZeneca D1441C00112 DB RCT International (43 sites)	Change in PANSS total score from baseline to Day 42; PANSS total (Baseline, Days 7 and 14), PANSS positive symptom and negative symptom subscale (Baseline, Days 7, 14, and 42), CGI Severity of Illness (Baseline, Days 7, 14, and 42), Children GAS (Baseline, Day 42), sum of PANSS items S1, S2, and S3 (Baseline, Days 7, 14, and 42); sum of PANSS items P4, P7, G8, and G14 scores (aggression/hostility cluster) and depression cluster subscale scores at baseline and Day 42, percentage of patients with response, defined as a ≥30% reduction from baseline in the PANSS total score at Day 42; CGI Global Improvement Score at Day 42.	Mean age (SD): 15.41 (1.32) years 58.6% male 61.4% Caucasian 12.3% black 18.2% oriental 8.2% other	Quetiapine 400 mg/day vs Quetiapine 800 mg/day vs Placebo DSM-IV diagnosis: Schizophrenia, disorganized: 8.2% vs 6.8% vs 6.8% Schizophrenia, paranoid: 72.6% vs 67.6% vs 71.2% Schizophrenia, residual: 0 vs 1.4% vs 0 Schizophrenia, undifferentiated: 19.2% vs 24.3% vs 21.9% v Mean PANSS score (SD): 98.1 (15.41) vs 97.7 (15.32) vs 97.2 (16.83) Mean PANSS Positive Symptom Subscale score (SD): 23.3 (5.80) vs 23.8 (4.84) vs 24.5 (5.57) Mean PANSS Negative Symptom Subscale score (SD) 25.4 (5.65) vs 25.8 (5.43) vs 24.8 (5.85) Mean Sum of PANSS Items S1, S2,and S3 scores (SD): 8.7 (3.86) vs 8.3 (3.74) vs 8.3 (3.98) Mean Children GAS score (SD): 43.4 (9.16) vs 42.6 (11.12) vs 41.8 (11.39)	NR/NR/268 enrolled and 222 randomized
AstraZeneca, Data on File, Study D1444C00132 DB RCT	PANSS total score; PANSS response rates, defined as a reduction of at least 30% from baseline PANSS total score; CGI Global Improvement rating ≤ 3; change in the CGI Severity of Illness score; change from baseline PANSS total score at all subsequent visits; change in PANSS positive, negative and general psychopathology subscales from baseline at all subsequent visits; change in PANSS aggression/hostility and PANSS depression clusters from baseline at all subsequent visits.	Placebo vs Quetiapine SR 400 vs 600 vs 800 vs Quetiapine IR 400 Mean age (SD): 34.1 (12.1) vs 34.1 (9.6) vs 34.2 (9.9) vs 34.4 (10.3) vs 34.4 (10.2) Male: 58.3% vs 70.3% vs 55.0% vs 59.8% vs 58.0% Caucasian: 59.1% vs 56.8% vs 59.5% vs 60.7% vs 59.7% Black: 4.3% vs 4.5% vs 3.6% vs 4.3% vs 5.9% Oriental: 36.5% vs 38.7% vs 36.0% vs 35.0% vs 34.5% Other: 0 vs 0 vs 0.9% vs 0	Placebo vs Quetiapine SR 400 vs 600 vs 800 vs Quetiapine IR 400 DSM-IV diagnosis, schizophrenic subtype n (%) --Disorganized: 5 (4.3) vs 8 (7.2) vs 5 (4.5) vs 5 (4.3) vs 2 (1.7) --Catatonic: 1 (0.9) vs 2 (1.8) vs 0 vs 1 (0.8) --Paranoid: 79 (68.7) vs 71 (64.0) vs 72 (64.9) vs 75 (64.1) vs 88 (73.9) --Undifferentiated: 30 (26.1) vs 30 (27.0) vs 34 (30.6) vs 37 (31.6) vs 28 (23.5) Mean PANSS (SD): 96.2 (13.3) vs 95.8 (13.9) vs 96.8 (14.1) vs 97.3 (14.7) vs 96.5 (16.0) Mean CGI severity of illness (SD): 4.9 (0.7) vs 4.9 (0.7) vs 4.9 (0.7) vs 5.0 (0.7) vs 4.9 (0.6)	NR/NR/588

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
AstraZeneca D1441C00112 DB RCT International (43 sites)	NR/NR/222	Quetiapine 400 mg/day vs Quetiapine 800 mg/day vs Placebo; *P* values are versus placebo Mean change PANSS total score: -27.31 (*P*=0.043) vs -28.44 (*P*=0.009) vs -19.15 Mean change PANSS positive symptom subscale score: -8.56 (*P*0.075) vs -9.34 (*P*=0.008) vs -6.51 Mean change PANSS negative symptom subscale score: -6.35 (*P*=0.239) vs -6.21 (*P*=0.245) vs -5.09 Mean change Sum of PANSS items S1, S2, and S3 scores: -2.58 (*P*=0.059) vs -2.39 (*P*=0.091) vs -1.51
AstraZeneca, Data on File, Study D1444C00132 DB RCT	142/NR/573	Placebo vs Quetiapine SR 400 vs 600 vs 800 vs Quetiapine IR 400 (*P* value is versus placebo) LS mean from baseline in PANSS total score: -18.8 vs -24.8 (*P*<0.05) vs -30.9 (*P*<0.001) vs -31.3 (*P*<0.001) vs -26.6 (*P*<0.01) PANSS response: 30.4% vs 44.1% (*P*<0.05) vs 60.4% (*P*<0.001) vs 56.4% (*P*<0.001) vs 52.9% (*P*<0.01) LS mean from baseline in CGI Severity of Illness score: -1.0 vs 1.3 vs -1.5 (*P*<0.001) vs -1.6 (*P*<0.001) vs -1.3 (*P*<0.05) CGI Global Improvement score, % of patients showing improvement: 60.0% vs 73.9% (*P*<0.05) vs 79.3% (*P*<0.01) vs 76.9% (*P*<0.01) vs 75.6% (*P*<0.05) Quetiapine SR 600 mg/day and SR 800 mg/day groups demonstrated significant improvement compared to placebo for the PANSS Negative symptom subscale score and PANSS depression cluster score at Day 42

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Author, year study design	Method of adverse effects assessment	Adverse effects reported
AstraZeneca D1441C00112 DB RCT International (43 sites)	Safety variables included the incidence and nature of AEs; changes from baseline to each visit, when measured, in clinical laboratory test results (eg, prolactin concentration) and ECG results; changes from baseline to each visit in vital signs, weight, and BMI; changes from baseline to each visit in SAS, BARS, and AIMS scores; and the incidence of anticholinergic medication use to treat emergent EPS.	Quetiapine 400 mg/day vs Quetiapine 800 mg/day vs Placebo Any AEs: 79.5% vs 74.3 vs 60.0% vs 71.2% Serious AEs: 5.5% vs 6.8% vs 5.3% vs 5.9% n (%) Somnolence: 20 (27.4) vs 22 (29.7) vs 5 (6.7) Headache: 6 (8.2) vs 16 (21.6) vs 14 (18.7) Dizziness: 6 (8.2) vs 11 (14.9) vs 4 (5.3) Dry mouth: 3 (4.1) vs 7 (9.5) vs 1 (1.3) Insomnia: 9 (12.3) vs 7 (9.5) vs 17 (22.7) Agitation: 6 (8.2) vs 6 (8.1) vs 10 (13.3) Tachycardia: 4 (5.5) vs 6 (8.1) vs 0 Increased appetite: 3 (4.1) vs 5 (6.8) vs 3 (4.0) Fatigue: 4 (5.5) vs 4 (5.4) vs 3 (4.0) Irritability: 2 (2.7) vs 4 (5.4) vs 0 Nausea: 3 (4.1) vs 4 (5.4) vs 13 (17.3) Sedation: 4 (5.5) vs 4 (5.4) vs 3 (4.0) Vomiting: 3 (4.1) vs 4 (5.4) vs 6 (8.0) Anxiety: 4 (5.5) vs 3 (4.1) vs 5 (6.7) Diarrhea: 4 (5.5) vs 1 (1.4) vs 4 (5.3) No AEs related to prolactin. No deaths. Changes in mean weight: +2.2 vs +1.8 vs -0.4 kg Changes in mean pulse rate: +6 vs +3.9 vs -1.4 beats per minute
AstraZeneca, Data on File, Study D1444C00132 DB RCT	Adverse events, laboratory measurements (clinical chemistry, hematology and urinalysis), ECG, vital signs (blood pressure and pulse rate), weight, BARS, SAR-S, use of anticholinergic medication, safety data with regards to diabetes mellitus including fasting glucose/insulin, glycosylated haemoglobin (HbA1c) and BMI and data for other specific safety areas (QT prolongation, metabolic risk factors, neutropenia/agranulocytosis, suicidality).	Placebo vs Quetiapine SR 400 vs 600 vs 800 vs Quetiapine IR 400 Adverse events n (%): 50 (42.4) vs 51 (45.1) vs 62 (54.9) vs 56 (46.3) vs 66 (53.7) Serious adverse events n (%): 2 (1.7) vs 2 (1.8) vs 3 (2.7) vs 1 (0.8) vs 6 (4.9) Death: 0 vs 0 vs 0 vs 0 vs 1 Insomnia n (%): 23 (19.5) vs 13 (11.5) vs 7 (6.2) vs 9 (7.4) vs 13 (10.6) Somnolence n (%): 2 (1.7) vs 8 (7.1) vs 10 (8.8) vs 14 (11.6) vs 9 (7.3) Dizziness n (%): 1 (0.8) vs 6 (5.3) vs 10 (8.8) vs 8 (6.6) vs 7 (5.7) Headache n (%): 8 (6.8) vs 6 (5.3) vs 4 (3.5) vs 4 (3.3) vs 2 (1.6) Sleep disorder n (%): 11 (9.3) vs 4 (3.5) vs 6 (5.3) vs 4 (3.3) vs 6 (4.9) Constipation n (%):5 (4.2) vs 2 (1.8) vs 6 (5.3) vs 5 (4.1) vs 1 (0.8)

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Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
AstraZeneca D1441C00112 DB RCT International (43 sites)	Quetiapine 400 mg/day vs Quetiapine 800 mg/day vs Placebo n(%) AEs associated with EPS: 9 (12.3%) vs 10 (13.5%) vs 4 (5.3%) Majority of patients showed no change in EPS as assessed by SAR-S, AIMS and BARS Incidence of anticholinergic medication use for treatment of emergent EPS: 5.48% vs 1.35% vs 0%	Total withdrawals: NR Withdrawals due to AEs: 14	
AstraZeneca, Data on File, Study D1444C00132 DB RCT	"Incidence of EPS-related adverse events was consistent across the quetiapine SR and IR groups and similar to placebo" Few patients using anticholinergic medication for symptoms of EPS in all groups Overall the assessment of parkinsonian and akathisia symptomatology as assessed by mean SAS and BARS scores indicated that quetiapine treatments were similar to placebo, and an improvement or no worsening in symptomatology in all active treatment groups	Placebo vs Quetiapine SR 400 vs 600 vs 800 vs Quetiapine IR 400 Total Withdrawals: 33 vs 30 vs 21 vs 31 vs 27 Withdrawals due to AEs: 3 (2.5%) vs 6 (5.3%) vs 3 (2.7%) vs 3 (2.5%) vs 6 (4.9%)	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
AstraZeneca D1444C00133, 2006 DB RCT Multicenter (40 sites) in U.S.	Inclusion: acutely ill male and females aged 18-65 diagnosed with DSM-IV schizophrenia; with PANSS total score >=70 and CGI-S >=4.	5 treatment groups (double-dummy): Quetiapine SR: 400 mg/day, 600 mg/day, 800 mg/day Quetiapine IR: 800 mg/day Placebo 6 weeks duration	NR	NR
Atmaca, 2003 Inpatients	Schizophrenia Exclusion: Co-morbid Axis I disorders, severe physical illness, history of alcohol/substance abuse, history of lipid-lowering treatment, presence of endocrinologic disorder, autoimmune, pulmonary, infectious diseases, neoplasms.	6 week study quetiapine(N=14): olanzapine(N=14): risperidone(N=14): clozapine(N=14): control group w/no treatment(N=11):	≥2 weeks	Biperiden hydrochloride, benzodiazepines
Azorin, 2001 DB, multicenter (France and Canada)	Diagnosis: schizophrenia (DSM-IV), Treatment-resistant: severe, chronic disease and poor response to previous neuroleptic drugs (no period of good functioning for ≥ 24 months despite use of two antipsychotic drugs; current episode without significant improvement for ≥ 6 months despite use of antipsychotic equivalent to haloperidol, 20 mg, for ≥ 6 weeks; total BPRS ≥ 45; CGI ≥ 4)	clozapine 200– 900 mg/day Mean dose 597.5 mg/day; risperidone 2–15mg/day Mean dose 8.3 mg/day individual dose titration Duration: 12 weeks	Single-blind placebo period of at least 3 days	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
AstraZeneca D1444C00133, 2006 DB RCT Multicenter (40 sites) in U.S.	Change in PANSS total score from baseline to Day 42 or end of treatment (LOCF). Response rates at end of treatment defined as reduction of >=30% from baseline PANSS total score; CGI-I <=3; Change in CGI-S at end of treatment; Change from baseline at all subsequent visits in PANSS total score; in PANSS positive, negative, and general psychopathology subscales; in PANSS aggression/hostility cluster; and in PANSS depression cluster.	Mean age 41 28.5% female 32.5% Caucasian 58.4% Black 1.3% Asian	82.7% paranoid subtype 14.5% undifferentiated subtype	Screened NR Eligible NR 565 enrolled
Atmaca, 2003 Inpatients	Positive and Negative Syndrome Scale (PANSS), body mass index (BMI), weight, fasting serum leptin and triglyceride levels: taken at baseline and endpoint	Mean age: 30.2 years 54.6% Female Ethnicity NR	29% psychotropic drug naïve	NR/NR/71
Azorin, 2001 DB, multicenter (France and Canada)	Leaving study early, relapse BPRS CGI-S PANSS total PANSS positive PANSS negative PANSS general psychopathology Calgary Depression Scale Psychotic Anxiety Scale Psychotic Depression Scale	Mean age 37.8 years 71% male Ethnicity NR	Mean PANSS score: 111 Mean BPRS score: 62 Mean CGI-S score: 5.5	NR/NR/273 olanzapine = 138 risperidone = 135

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
AstraZeneca D1444C00133, 2006 DB RCT Multicenter (40 sites) in U.S.	232 (42.6%) withdrew Lost to followup NR 544 (96.2%) analyzed	Placebo vs Quetiapine SR 400 mg vs SR 600 mg vs SR 800 mg vs IR 800 mg/day: PANSS total score, LS mean change from baseline: -12.1 vs -13.8 vs -16.8 vs -14.8 vs -15.0 Quetiapine SR at each of the 3 doses and quetiapine IR 800 mg/day were not statistically superior to placebo. PANSS response, % of patients responding (>=30% improvement in PANSS total score): 20.7 vs 19.5 vs 26.7 vs 23.6 vs 22.9 CGI-S, LS mean change from baseline: -0.5 vs -0.6 vs -0.6 vs -0.6 vs -0.6 CGI-I, % of patients showing improvement (defined as much improved, improved, and minimally improved): 56.8 vs 65.5 vs 67.3 vs 62.7 vs 61.5. On improvement there was no superiority to placebo for any of the quetiapine dose groups. No differences between quetiapine IR 800 mg/day and placebo on any outcome.
Atmaca, 2003 Inpatients	NR/NR/64	Mean scores changes at Endpoint: Quetiapine: Body weight: 4.41; (p<.05), PANSS score: (p<.01), BMI: (P=.26) Olanzapine: Body weight: 8.92; (p<.01), PANSS score: (p<.001), BMI: (p<.05) Risperidone: Body weight: 0.54; (P=.91), PANSS score: (p<.01), BMI: (P=.71) Clozapine: Body weight: 6.52; (p<.01), PANSS score: (p<.01), BMI: (p<.05) No treatment/control group: Body weight: -1.32; (P=.82), PANSS score: (p<.01), BMI: (P=.62)
Azorin, 2001 DB, multicenter (France and Canada)	72/3/256	Mean change from Baseline to 12 weeks (ITT) clozapine/risperidone: BPRS: -23.3/-17.7 (ANCOVA p = 0.006) CGI-S: -1.8/-1.4 (p = 0.008) PANSS total:-37.5/-29.9 (p = 0.02) PANSS positive: -10.4/-8.3 (p = 0.02) PANSS negative: -8.8/-7.1 (p = 0.06) PANSS general psychopathology: -18.3/-14.1 (p = 0.008) Calgary Depression Scale: -3.2/-2.3 (p = 0.10) Psychotic Anxiety Scale: --18.5/-13.5 (p = 0.02) Psychotic Depression Scale: -24.8/-20.2 (p = 0.15) Responders (Kane criteria): 48.4%/43.1% (p<0.38) Improvement in BPRS of 20%, 30%, 40%: SS C>R, 50% NS

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Author, year study design	Method of adverse effects assessment	Adverse effects reported
AstraZeneca D1444C00133, 2006 DB RCT Multicenter (40 sites) in U.S.	Reporting of AEs, labs (clinical chemistry, hematology, and urinalysis), ECG, vital signs, weight, BARS, SAS, use of anticholinergic medication, data on diabetes mellitus (fasting glucose, HbA1C), BMI, others incl. Suicidality, neutropenia/agranulocytosis, metabolic risk factors, QT prolongation	Placebo vs Quetiapine SR 400 mg vs SR 600 mg vs SR 800 mg vs IR 800 mg/day, % of group: Dry mouth: 2.6 vs 21.1 vs 17.1 vs 17.7 vs 16.5 Sedation: 9.4 vs 21.1 vs 17.1 vs 13.3 vs 21.7 Somnolence: 2.6 vs 16.7 vs 10.5 vs 13.3 vs 14.8 Dizziness: 6.8 vs 12.3 vs 9.5 vs 7.1 vs 9.6 Headache: 15.4 vs 10.5 vs 6.7 vs 10.6 vs 8.7 Constipation: 7.7 vs 7.9 vs 4.8 vs 8.0 vs 7.8 Dyspepsia: 10.3 vs 7.9 vs 3.8 vs 1.8 vs 0.9 Arthralgia: 1.7 vs 6.1 vs 0 vs 1.8 vs 1.7 Psychotic disorder: 4.3 vs 6.1 vs 3.8 vs 1.8 vs 1.7 Agitation: 6.0 vs 5.3 vs 5.7 vs 2.7 vs 3.5 Fatigue: 0 vs 3.5 vs 4.8 vs 2.7 vs 5.2 Nausea: 8.5 vs 3.5 vs 6.7 vs 6.2 vs 4.3 Schizophrenia: 1.7 vs 3.5 vs 5.7 vs 5.3 vs 4.3 Diarrhea: 1.7 vs 1.8 vs 1.9 vs 5.3 vs 6.1 Stomach discomfort: 2.6 vs 1.8 vs 1.0 vs 2.7 vs 5.2 Vomiting 5.1 vs 1.8 vs 3.8 vs 7.1 vs 2.6
Atmaca, 2003 Inpatients	weight, body mass index, fasting serum leptin and triglyceride levels taken at baseline and endpoint	NR
Azorin, 2001 DB, multicenter (France and Canada)	Blood counts weekly, vital signed daily x 11 days, then periodically. EPS rated by ESRS every 2 weeks Adverse events recorded.	Adverse Effects Reported: clozapine 78.7% risperidone 82.8% (P=0.44) AEs SS more frequent: clozapine: convulsions, dizziness, sialorrhea, tachycardia, somnolence risperidone: EPS, insomnia, dry mouth

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Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
AstraZeneca D1444C00133, 2006 DB RCT Multicenter (40 sites) in U.S.	A slight increase in EPS-related AEs occurred in quetiapine SR 800 mg/day and IR 800 mg/day compared with placebo. No other details specified.	232 withdrawals; 60 withdrew due to AE	
Atmaca, 2003 Inpatients	NR	NR; NR	
Azorin, 2001 DB, multicenter (France and Canada)	AEs SS more frequent: clozapine: convulsions, dizziness, sialorrhea, tachycardia, somnolence risperidone: EPS, insomnia, dry mouth	Overall 72 (26%) Due to adverse events: 28 (10%) clozapine: 11.6%, risperidone 10.3%	BPRS score extracted from PANSS score

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Bai, 2006 Single-blind, RCT, single center (Taiwan)	Symptomatic stable hospitalized patients 18-65 w/ DSM IV diagnosis of schizophrenia treated for 3 months with oral risperidone, good health Exclusion due to neuroleptic malignant syndrome, organic disease of the CNS and seizure disorder; violent behavior; suicide risk.	Oral risperidone: 2-6 mg/day Long-acting risperidone: 20-50 mg every 2 weeks Duration: 12 weeks active treatment	3 months treatment with oral risperidone	Anticholinergics and benzodiazepines
Bellack, 2004 DB, substudy within larger trial	Patients with schizophrenia or schizoaffective disorder, including those with adjunctive medications or history of poor compliance and substance abuse; at least two previous trials of a conventional antipsychotic at doses equivalent to 600 (1st trial) and 250-500 (2nd trial) mg/day chlorpromazine; and a rating of at least moderate on BPRS or SANS subscales	clozapine: 500mg/day; max 800 mg/day after 5 weeks risperidone: 6 mg/day, max 16 mg/day after 5 weeks Duration: 29 weeks	None	Not specified
Bender, 2006 (Companion to Naber 2005) DB, RCT - sub sample	Inclusion- considered for clozapine therapy, i.e. they had a documented history that they had either failed to respond to at least one antipsychotic other than clozapine and olanzapine or had experienced intolerable side-effects during these prior antipsychotic treatments, 18 to 65 years and a normalized BPRS score of at least 24 at baseline. Exclusion- pregnant or lactating and a history of substance abuse or dependence within the past 3 months and serious, unstable somatic illnesses, previous use of olanzapine and/or clozapine	subsample of 54 patients from 114 [olanzapine (*n* = 30) vs. clozapine (*n* = 24) for 24 weeks	2-9 days	benzodiazepines for agitation (lorazepam up to 8 mg/d, diazepam up to 60 mg/d, oxazepam up to 100 mg/d, temazepam up to 30 mg/d) or chloral hydrate up to 1500 mg/d for insomnia, and biperiden up to 6 mg/d for treatment-emergent EPS.

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Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Bai, 2006 Single-blind, RCT, single center (Taiwan)	PANSS and CGI severity at baseline and at weeks 4, 8 and 12	Mean age: 46.4 Male: 50% Ethnicity: NR	Risperidone long-acting injection vs oral risperidone PANSS Total 65.2 ± 17.6 vs 70.2 ± 19.6 CGI-S 3.96 ± 0.20 vs 3.92 ± 0.28 GAF 64.4 ± 10.4 vs 59.6 ± 11.4	NR/NR/50
Bellack, 2004 DB, substudy within larger trial	Maryland Assessment of Social Competence, Wisconsin Card Sorting Test, and SANS symptoms ratings tests, Proportion stopping early due to lack of efficacy. Administered at baseline, Week 17, and Week 29. Patient responses were videotaped for coding by blinded raters on verbal behavior	Not specified for full study population. Of 72 subjects assessed for social competence at baseline: mean age 41.4 years 73% male 58% Caucasian	Illness	NR/NR/107 enrolled Number per group NR
Bender, 2006 (Companion to Naber 2005) DB, RCT - sub sample	Executive functioning was measured using computerized versions of the Stroop test, the Tower of London test (ToL) and the Short Wisconsin Card Sorting test. Assessed following a 2- to 9-day washout and again after 4 and 26 wk of neuroleptic treatment.	Mean age 33 years 67% male Ethnicity: NR	Age of onset 25.2 years	NR/NR/54

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Bai, 2006 Single-blind, RCT, single center (Taiwan)	1/NR/49	Change from baseline - Long acting risperidone vs. regular risperidone Total PANSS -0.16 vs. -2.4 P=NS Negative -0.64 vs. 0.08 P=NS Positive 0.72 vs. -1.24 P=0.022 CGI-S -0.08 vs. -0.04 P=NS Side effects UKU -2.12 vs. -0.13 P=0.037
Bellack, 2004 DB, substudy within larger trial	Total loss to f/u: 47% (MASC), 66% (WCST) Loss of efficacy: 36% Subject withdrawal 32% Adverse reactions 17% Number of withdrawals varied and crossover by test administered.	Symptoms: Change in CGI: risperidone: -1.42 (95%CI -1.93 to -0.99); clozapine: -1.48 (95%CI -2.11 to -0.99) Withdrawal due to lack of efficacy: 38% of risperidone 15% of clozapine (SS different, p-value NR) Social Skill and Problem Solving: At week 29: risperidone: SS decrease in perseverative errors clozapine: SS decrease in verbal score Change in Effect Size for verbal behavior: risperidone: 0.33 (95%CI: 0.01to 0.79); clozapine: -0.037 (95%CI -0.47 to 0.30).
Bender, 2006 (Companion to Naber 2005) DB, RCT - sub sample	23/NR/31	Schizophrenia symptoms, extrapyramidal side-effects and cognitive performance improved significantly in the course of either drug treatment. Stroop test performance and Tower of London planning time improved significantly over 26 wk compared to baseline and 4-wk follow-up assessment while Wisconsin Card Sorting and Tower of London execution time improved significantly after 4 wk with no further improvement after 26 wk. Improved executive function was not related to improving positive symptoms and easing extrapyramidal side-effects, thus indicative of a primary treatment effect of either antipsychotic. However, Stroop reaction time improved with olanzapine while clozapine had a stronger effect on improving negative symptoms, thus suggestive of a differential drug effect.

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Author, year study design	Method of adverse effects assessment	Adverse effects reported
Bai, 2006 Single-blind, RCT, single center (Taiwan)	UKU	See results
Bellack, 2004 DB, substudy within larger trial	NR	NR
Bender, 2006 (Companion to Naber 2005) DB, RCT - sub sample	NR	NR

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Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Bai, 2006 Single-blind, RCT, single center (Taiwan)	Risperidone long-acting injection vs Oral risperidone change from BL AIMS: -3.20 ± 4.7 vs -4.36 ± 3.9 BARN:-0.04 ± 1.74 vs -0.2 ± 1.11 SAS: -3.50 ± 5.57vs -2.95 ± 5.82	1 and 1	
Bellack, 2004 DB, substudy within larger trial	NR	17% of withdrawals due to AE's but numbers per drug not clear	While some differences are apparent between drugs on results for verbal score and problem solving, changes were not considered clinically important by authors. Lack of ITT, low power, and poor reporting make result difficult to interpret or generalize.
Bender, 2006 (Companion to Naber 2005) DB, RCT - sub sample	SAS Olanzapine vs. clozapine n=31 Baseline 0.5(0,5) vs.0.6(0.4) 26 weeks 0.2(0.2) vs 0.1 (0.1)	23 withdrawals	Completers analysis.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Bitter, 2004 RCT, Multicenter (Hungary & South Africa)	Hospitalized patients 18-65 yrs, with schizophrenia; minimum BPRS score (items 1-7) of 42, and have failed to respond to standard treatment with typical antipsychotics (at least 1 trial of 4-6 wks, 400-600mg chlorpromazine or equivalents) due to insufficient effectiveness or intolerable side effects	180 18 weeks	2-9 days	Episodic use of benzodiazepines not allowed, stable doses of chronically used benzodiazepines allowed with max doses, anticholinergic meds to treat new or worsening EPS allowed but all other uses not allowed
Bondolfi, 1998 DB, RCT, single-center Inpatients	Chronic schizophrenia (DSM-II-R); Treatment-resistant: failed to respond or intolerant of ≥ 2 different classes of antipsychotic drugs in appropriate doses for ≥ 4 weeks each; total PANSS 60–120	clozapine: 150–400 mg/day mean 291 mg/day; risperidone: 3–12 mg/day mean 6.4 mg/day Duration: 8 weeks	3-7 days depending on psychotic symptoms	lorazepam and oxazepam (sleep induction), biperiden and procyclidine (EPS), clothiapine (emergency treatment) as required
Breier, 1999 DB, RCT, single-center (NIH Clinical Center) Unclear if inpatient	Diagnosis: schizophrenia (DSM-IV); Partial response to neuroleptic drugs: (i) history of residual positive and/or negative symptoms after ≥ 6 week trial of therapeutic dose of neuroleptic agent; (ii) at least minimum level of positive (4 positive BPRS items > 8) and/or negative (SANS score > 20) symptoms at time of evaluation for study; (iii) at least minimum level of positive and negative symptoms after prospective trial of ≥ 2 weeks of fluphenazine, 20 mg/day (range 10–30 mg/day)	clozapine: 200–600 mg/day; fixed dose mean 403.6 mg/day; risperidone: 2–9 mg/day; fixed dose mean 5.9 mg/day Duration: 6 weeks fluphenazine treatment for ≥ 2 weeks; then, 66% patients underwent drug-free period	Mean 18 days	benztropine mesylate (EPS) as required

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Bitter, 2004 RCT, Multicenter (Hungary & South Africa)	PANSS CGI 19 visits over 20 weeks Kane criteria for Response: BPRS(1-7) improvement >20% +CGI-S <3 or BPRS(1-7) final score <35 Other assessments of Response: PANSS total score: >/= 20%, 30%, 40% or 50%	Mean age 38 48% white 60% male	Not reported, stated to have NS differences	189/150/147
Bondolfi, 1998 DB, RCT, single-center Inpatients	Leaving study early Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression (CGI) taken at baseline and endpoint	Mean age: 37.2 years 70.9% Male Ethnicity NR	Mean age at onset: 23 years Mean age at first hospitalization: 26 years Mean # hospitalizations 6.1 Mean # months in hospital: 36.6 100% inpatient Schizophrenia type: paranoid: 58% disorganized: 27.9% undifferentiated: 8.1% residual: 5.8%	NR/NR/86 clozapine: 43 risperidone: 43
Breier, 1999 DB, RCT, single-center (NIH Clinical Center) Unclear if inpatient	Leaving study early Physiological monitoring (laboratory tests) Mental state (BPRS; SANS; Hamilton Rating Scale – depression)	Mean, age: 35.0 years, range 18–55 years 66% male Ethnicity NR	History: duration of illness, about 12.5 years; chronic schizophrenia; partial response to neuroleptic drugs*	NR/NR/29

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Bitter, 2004 RCT, Multicenter (Hungary & South Africa)	7/NR/140 for efficacy assessments 62/NR/147 for safety assessments	Change in PANSS total: clozapine -37.9 olanzapine -37.7 (NS) Change in PANSS positive clozapine -11.8 olanzapine -11.7 (NS) Change in PANSS negative clozapine -7.7 olanzapine -7.6 (NS) Change in CGI-S clozapine -1.5 olanzapine -1.4 (NS) Kane criteria: clozapine 60.8% olanzapine 57.9% (NS) PANSS criteria for Response: NS differences between groups Discontinue study due to lack of efficacy: clozapine 4.2% olanzapine 5.3%
Bondolfi, 1998 DB, RCT, single-center Inpatients	18/0/86	Clozapine vs risperidone (p value) Proportion with 20% improvement: 67% vs 65% (p = 0.30) Mean Change at 8 weeks (ITT) All NS PANSS total: -23.2 vs -27.4 PANSS positive: -6.7 vs -8.3 PANSS negative: -6.1 vs -6.0 PANSS general psychopathology: -10.4 vs 12.2 Survival Analysis indicated risperidone patients responded faster than clozapine patients
Breier, 1999 DB, RCT, single-center (NIH Clinical Center) Unclear if inpatient	NR/NR/29	Mean Change in score (clozapine/risperidone, p value) BPRS total:-6.36/-4.73 (P= 0.19) BPRS Positive symptoms: -2.5/-1.0 (P= 0.04) BPRS Responders (20% improvement): 35.7%/20% (P= 0.34) SANS: -2.14/4.4 (P= 0/54) HAM-D: -4.5/-1.92 (P= 0.25)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Bitter, 2004 RCT, Multicenter (Hungary & South Africa)	EPS measured by: SAS, AIMS, and HAS scales Adverse events reported by patients categorized by COSTART dictionary Lab tests, weight, ECG also monitored	clozapine, olanzapine, p-value Weight gain: 9.5%, 9.2%, P=0.958 Mean change in weight: NS Somnolence: 14.9%, 2.6%, P=0.008 Dizziness: 8.1%, 1.3%, P=0.049 Hypersalivation: 6.8%, 1.3%, P=0.089 Postural hypotension: 5.4%, 1.3%, P=0.163 Back Pain 0.0%, 5.3%, P=0.045 NS difference on CBC parameters EPS: Baseline to Endpoint on SAS, AIMS, or HAS: NS difference Treatment emergent akathisia (HAS >/= 3) or dyskinesia: NS Difference Treatment emergent parkinsonism: not reported in either group
Bondolfi, 1998 DB, RCT, single-center Inpatients	Patient self-report EPS symptoms (Extrapyramidal Symptom Rating Scale: ESRS): endpoint mean values and SDs not reported Other adverse events: UKU, mean endpoint data and SDs not reported	Adverse effects reported, risperidone vs clozapine: Asthenia/lassitude/increased fatigability: 28% vs 51% (p<0.05) Weight gain: 23% vs 37% (P=0.24) Sleepiness/sedation: R: 30% vs C: 47% (NS) Failing memory: R: 21% vs C: 35% (NS) Concentration difficulties: R: 16% vs C: 26% (NS) Increased duration of sleep: R: 19% vs C: 21% (NS) Nausea/vomiting: R: 16% vs C: 21% (NS) Orthostatic dizziness: R: 12% vs C: 21% (NS) Reduced duration of sleep: R: 14% vs C: 7% (NS) Diminished sexual drive: R: 9% vs 5% (NS)
Breier, 1999 DB, RCT, single-center (NIH Clinical Center) Unclear if inpatient	SAR-S; neuroendocrine serum level monitoring	Mean change in SAR-S clozapine: -0.93 risperidone: +0.26 (P=0.05) Mean Change in serum Prolactin: clozapine: -41.1ng/ml risperidone: +11.8 (P=0.001) Growth Hormone, cortisol: changes NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Bitter, 2004 RCT, Multicenter (Hungary & South Africa)	EPS: Baseline to Endpoint on SAS, AIMS, or HAS: NS difference Treatment emergent akathisia (HAS >/= 3) or dyskinesia: NS Difference Treatment emergent parkinsonism: not reported in either group	Overall: 85 (58%) Due to adverse events: clozapine 7 olanzapine 7	Refractoriness includes intolerance, does not use Kane criteria.
Bondolfi, 1998 DB, RCT, single-center Inpatients	EPS: "No significant difference between the groups at endpoint in the mean total ESRS scores, the different cluster scores, or the different cluster scores on the parkinsonism scales" - data not reported Proportion scoring 0 (clozapine vs risperidone) at week 8 on ESRS: Total with 0 on ESRS total score: 37% vs 54% (NS) % with 0 on ESRS parkinsonism score: 37% vs 61% (p = 0.03) % with 0 on ESRS dystonia: 98% vs 95% (NS) % with 0 on ESRS dyskinesia: 84% vs 84% (NS)	Overall 18 (21%) Due to adverse events: 2.3% (2.3% in each group)	Differences at baseline: # months in hospital, PANSS positive; analyses presented focus on within group differences more than between group comparisons. Dose of clozapine low.
Breier, 1999 DB, RCT, single-center (NIH Clinical Center) Unclear if inpatient	Clozapine vs risperidone: Simpson-Angus Rating Scale Mean Change: -8 vs 2, P=0.05	NR/NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Breier, 2005 DB, parallel-group 28 week RCT, multicenter (Europe, North and South America) Inpatients and outpatients	Schizophrenia (DSM-IV); baseline score of 42 or higher on BPRS; score of 4 or higher on at least one positive symptom item of the Positive and Negative Syndrome Scale; score of 4 or higher on CGI	olanzapine: 5-20 mg/daily (mean: 15.27) ziprasidone 40-160 mg/day (mean: 115.96)	2-9 days (single-blind placebo lead in period)	lorazepam (≤4 mg/day); benzodiazepine or hypnotic monotherapy during study period 2 (≤10 mg/day of diazepam equivalents recommended). Benztropine mesylate or biperiden up to 6 mg/day if EPS occurred or existed at visit 1.
Byerly, 2008 DB RCT 5 Dallas County public mental health outpatient clinics	Outpatients (n=42, age ≥18 years) with schizophrenia or schizoaffective disorder who experienced risperidone-associated sexual dysfunction.	Risperidone mean dose=4.1 mg (1.2) n=22 Quetiapine mean dose=290.0 mg(55.2) n=20 6 weeks	Cross taper for 1st week for patients randomized to quetiapine	Yes- antidepressants

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Breier, 2005 DB, parallel-group 28 week RCT, multicenter (Europe, North and South America) Inpatients and outpatients	Primary: Positive and Negative Syndrome Scale Secondary Efficacy measurements: Positive and Negative Syndrome Scale subscales, general psychopathology, cognition, and excitability. Symptom exacerbation and time to exacerbation: Positive and Negative Syndrome Scale and CGI severity of illness scale. Heinrichs-Carpenter QOL. Pts were seen weekly for the first 2 months and 7 additional times thereafter.	mean age: O: 40.1 ± 11.6; Z: 38.2 ± 12.1; P=0.04 Gender (%) male: O: 180 (65%); Z: 172 (63.5%) Caucasian: 43.6% African descent 26.3% Hispanic: 22.6% Other: 7.5%	Mean Age at onset of disease years: O: 23.9; Z: 22.8 Number of previous episodes, n O: 7; Z: 7.2 Baseline Positive and Negative Syndrome Scale total score: O: 99.8; Z: 102	NR/NR/548
Byerly, 2008 DB RCT 5 Dallas County public mental health outpatient clinics	Arizona Sexual Side Effects (ASEX) scale at baseline and weeks 2, 4 and 6	Mean age 42.3 yrs 52.4% male Ethnicity NR	Risperidone vs. quetiapine ASEX total at baseline, M (S.D.) 22.4 (4.6) vs. 22.8 (5.1) PANSS total at baseline, M (S.D.) 78.2 (12.2) vs. 74.1 (12.2) PANSS total at week 6, M (S.D.) 72.1 (6.2) vs. 71.5 (6.2)	NR/NR/42

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Breier, 2005 DB, parallel-group 28 week RCT, multicenter (Europe, North and South America) Inpatients and outpatients	268 (discontinued) / 24/280 Lack of efficacy (O: 20 vs. Z 37 , P=0.02) and aggravation of psychosis (O: 4 vs. Z: 12, P=0.05)	SANS summary score, mean change from baseline: O -6.0 v R -4.7; P=0.0151; effect size 0.34 Affective flattening, mean change from baseline: O -9.1 v R -6.5; P=0.0065; effect size 0.39 Speech difficulty, mean change from baseline: O -5.2 v R -4.2; P=0.0747;
Byerly, 2008 DB RCT 5 Dallas County public mental health outpatient clinics	6/6/36	ASEX at week 6 (SD) Risperidone 20.53 (5.78) vs. quetiapine 18.51 (5.69) P = 0.30

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Breier, 2005 DB, parallel-group 28 week RCT, multicenter (Europe, North and South America) Inpatients and outpatients	Montgomery-Asberg Depression Rating Scale and Hamilton Anxiety Rating Scale	Montgomery Asberg Depression Rating Scale: LOCF: Mean Chg in Score at 28 wk: O: (n=270) vs. Z: (n=260) (difference btw groups) -7.1 vs. -5.5 (p =0.05) 7.5 vs. 8.1 (p= NS) ---using Mixed-Effects Model Hamilton Anxiety Rating Scale: LOCF Mean Chg in Score at 28 wk O (n=270) vs. Z (n=261) -5.8 vs. -4.3 (p=0.002) 4.5 vs. 5.2, (p=NS)-using Mixed-Effects Model Adverse Event: Treatment-Emergent AE in 28 week: O: (n=277) ; Z: (n=271) AE: statistically different rates or occurred in at least 10%): O: % vs. Z: %; p Any: 75.1% vs. 80.4%; NS Headache, Anxiety, Anorexia, all NS Weight increase: 12.6% vs. 1.8%; <0.001 Appetite increase: 7.2% vs. 1.8%; 0.02 Insomnia: 6.9% vs. 22.1%; <0.001 Vomiting: 4% vs. 9.2%; 0.02 Dystonia: 0 vs. 2.2%; 0.02 Hypotension: 0 vs. 1.8%; 0.03 Weight (kg): LOCF: Mean Change in Value at 28 wk: O:(n=269) vs. Z:(n=260) (diff btw groups) 3.06 vs. -1.12 (p<0.001) Mean Fasting gluc. (mmol/liter): LOCF: Mean Chg at 28 wk: O: (n=228) vs. Z: (n=219) 0.28 vs. -0.01 (NS) TC (mmol/liter): LOCF: Mean Chg at 28 wk: O: (n=215) vs. Z: (n=203) 0.08 vs. -0.33 (p<0.002) HDL (mmol/liter): LOCF Mean Chg at 28 wk: O: (n=212) vs. Z: (n=201) -0.06 vs. 0.02 (p<0.001) LDL (mmol/liter): LOCF Mean Chg at 28 wk O: (n=204) vs. Z: (n=196) 0.02 vs. -0.27 (p=0.02) TG (mmol/liter): LOCF Mean Chg at 28 wk O: (n=215) vs. Z: (n=203) 0.39 vs. -0.24 (p<0.001) Prolactin level (pmol): LOCF Mean Chg at 28 wk: O: (n=250) vs. Z: (n=241) 0.20 vs. 0.38 (NS) QTc interval (msec): LOCF Mean Chg at 28 wk: O: (n=270) vs. Z: (n=259) 4.81 vs. 5.58 (NS)
Byerly, 2008 DB RCT 5 Dallas County public mental health outpatient clinics	NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Breier, 2005 DB, parallel-group 28 week RCT, multicenter (Europe, North and South America) Inpatients and outpatients	Simpson-Angus Rating Scale: Mean Change in Score BL to Endpoint: O: (n=268) vs. Z: (n=260) Difference btw. groups: -1.16 vs. -0.82 (p=NS) Baseline to maximum: -0.05 vs. 0.62 (p<0.001) Barnes Rating Scale for Drug-Induced Akathisia, Mean Change in Score BL to Endpoint: O (n=270) vs Z (n=260) Difference btw. groups: -0.21 vs. -0.10 (p=0.04) Baseline to maximum: 0.19 vs. 0.30 (p=0.03) Abnormal Involuntary Movement Scale: Mean Change in Score BL to Endpoint: O (n=268) vs. Z (n=261) Difference btw. groups: -0.53 vs. -0.45 (p=NS) Baseline to maximum: 1.47 vs. 1.83 (p=0.01) Use of BZD: Z 53.5% vs. O: 40.4 %, p=0.003. More Z pts took BZD for 1-14 days than O (22.9% vs. 14.8%, p=0.02) but not for durations >14 days (30.6% vs. 25.6%, p=0.22). More Z pts than O pts received at least one dose of an anticholinergic (15.5% vs. 7.2%, p=0.003). More Z pts took an anticholinergic than O pts for 1-14 days (8.9% vs. 1.4%, p<0.001 but not for duration > 14 days (6.6% vs. 5.8%, p=0.73).	268 (discontinued) / 73 (O: 32, Z: 41)	Compliant with study drug regimen: O: 97.8% vs. Z 94.9%; p<0.001 Because there was a higher percentage of dropouts in the Z group, the analysis with the LOCF may have had a greater likelihood of detecting a SS difference in the case of smaller effect sizes that favor O.
Byerly, 2008 DB RCT 5 Dallas County public mental health outpatient clinics	NR	6 withdrawals due to AEs NR	Completers analysis.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Canive, 2006 DB, RCT, crossover	Inpatients 18-65 yrs.; met DSM-IV criteria for schizophrenia determined by SCID-I; rating at screening of moderate or greater on at least 1 of 4 PANSS psychoticism screening items; decrease in PANSS total score between screen and baseline of no more than 20 points; PANSS total score at baseline with a minimum level of severity of 60; rating at screening of moderate or greater on CGI Severity of Illness item; good health; negative urine drug screen and no history of alcoholism or drug abuse in 3 months prior to enrollment; no other psychotropic medications	olanzapine: avg. dose 15 mg/day risperidone: avg. dose 6 mg/day Duration: Two 8 week treatment phases	10 days for each active treatment phase	NR
Canuso 2009 DB RCT India, Russia, the Ukraine, and the United States Inpatient	Inclusion: 18 to 65 years; schizophrenia (paranoid, disorganized, or undifferentiated types); acute exacerbation < 4 weeks but > 4 days; symptom scores ≥4 (at least moderate) on at least two of the PANSS items of hostility, excitement, tension, uncooperativeness, and poor impulse control, and a total combined score ≥17 for these items; a score ≥5 (at least markedly ill) on CGI-S and were hospitalized or required hospitalization. Exclusion: DSM-IV axis I diagnosis (except for schizophrenia and substance abuse); an axis II diagnosis of mental retardation or borderline personality disorder; acute psychotic symptoms explained by substance use or medical illness; evidence for imminent risk of self-harm; a history of treatment resistance; treatment with quetiapine, paliperidone extended-release, or risperidone for 7 or more days prior; sensitivity to paliperidone extended-release, risperidone, or quetiapine; depot antipsychotic treatment within one cycle before baseline; and ECT within 3 months	Paliperidone extended-release (mean 9.8 mg), quetiapine (599.1 mg), or placebo for 6 weeks	None	After 1st 14 days, the additive-therapy phase, any psychotropic medication, including antipsychotics, was permitted

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Canive, 2006 DB, RCT, crossover	PANSS, SANS, CGI, Calgary Depression Scale, AIMS, BARNES, Simpson-Angus Scale (SAS), Ray Visual and Auditory learning task, APT, Verbal Fluency (CFL), WMS-R, Digit Span forward and backward (WAIS-R), WCST, and Trails Making Tests Part A and B Baseline and weeks 1, 8, and 18	Mean age: 42 yrs Gender: NR Ethnicity: NR	NR	NR/NR/15
Canuso 2009 DB RCT India, Russia, the Ukraine, and the United States Inpatient	PANSS, the severity and change scores of the Clinical Global Impressions scale (CGI-S and CGI-C, respectively) (14), and a composite response measure (a PANSS total score reduction ≥30% and a CGI-C score of 1 or 2 [very much or much improved]). Assessments were performed at baseline (except for the CGI-C), on days 3, 5, 7, 9, 14, 21, 28, and 42, and at endpoint.	36 yrs old 66% male 45% Caucasian 37% Asian 16% Black 1% Hispanic 1% other	Paranoid 91% Undifferentiated 6% Disorganized 3%	NR/NR/399

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Canive, 2006 DB, RCT, crossover	6 withdrawn/9 analyzed	Improvement occurred on most negative and positive symptom scales regardless of assigned medication. Main effects and/or linear trends found for PANSS positive, PANSS negative, PANSS general, PANSS total, CGI severity, SANS alogia, SANS anhedonia, SANS attention, SANS avolition, and SANS total scores. For PANSS positive and CGI, all improvements occurred between week 1 (unmedicated) and week 8 (end of 1st drug treatment phase) and remained constant between week 10 and week 18. Both medications led to significant improvements on al PANSS subscales; olanzapine led to greater improvements on PANSS General and PANSS Total; means for all scales followed pattern of olanzapine being more efficacious than risperidone; CGI scores improved during first treatment period and held steady during second. Both medications led to significant improvements in SANS Anhedonia, SANS Avolition, SANS Attention, SANS Alogia, and SANS total scores; olanzapine led to greater improvements on SANS Attention; means for all scales followed pattern of olanzapine being more efficacious; olanzapine also more effective for treating negative symptoms as shown by analysis performed using all SANS subscales and the PANSS negative subscale. No improvements found on movement rating scales, with no main effects or interactions for AIMS, Barnes, and Simpson-Angus scales (all Fs <1.4, Ps >0.27). Both medications showed consistent improvement across assessments at weeks 1, 8, and 18 in scores for memory storage, attention, and verbal fluency; no significant improvements in test scores for working memory; no difference between medications seen for any of the neuropsychologic test scores.
Canuso 2009 DB RCT India, Russia, the Ukraine, and the United States Inpatient	116/21/394 it and 397 safety Withdrawals by group Paliperidone 34 (21.3%) Quetiapine 53 (33.3%) Placebo 29 (36.3%)	Between-Group Least-Squares Mean Differences in Change Scores on Efficacy Measures (SE) at 42 days Paliperidone vs. Quetiapine / Paliperidone vs. Placebo / Quetiapine vs. Placebo PANNS total –4.7* (2.0) / –7.8* (2.5) / –3.1 (2.5) Positive subscore –1.1 (0.6) / –1.9*(0.8) / –0.8 (0.8) Negative subscore –1.2* (0.5) / –2.1* (0.6) / –1.0 (0.6) CGI-S –0.3*(0.1) / –0.5* (0.1) / –0.2 (0.1) CGI-C –0.1 (0.1) / –0.4* (0.2) / –0.3 (0.2) * P < 0.05

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Canive, 2006 DB, RCT, crossover	NR	NR
Canuso 2009 DB RCT India, Russia, the Ukraine, and the United States Inpatient	Treatment emergent adverse events and vital signs were monitored and recorded at each visit. Laboratory tests were conducted on days 0, 14, and 42. Movement disorders were assessed on days 0, 14, and 42 using the Simpson-Angus Rating Scale , the Barnes Rating Scale for Drug-Induced Akathisia (18), and the Abnormal Involuntary Movement Scale	Paliperidone vs. quetiapine vs. placebo Participants with at least one adverse event 119 (75.3) vs. 123 (77.4) vs. 54 (67.5) Gastrointestinal disorders Constipation 7 (4.4) vs. 12 (7.5) vs. 2 (2.5) Diarrhea 2 (1.3) vs. 8 (5.0) vs. 2 (2.5) Dry mouth 5 (3.2) vs. 10 (6.3) vs. 1 (1.3) Dyspepsia 4 (2.5) vs. 8 (5.0) vs. 4 (5.0) Vomiting 12 (7.6) vs. 10 (6.3) vs. 2 (2.5) General disorders Asthenia 10 (6.3) vs. 8 (5.0) vs. 6 (7.5) Weight increase 5 (3.2) vs. 9 (5.7) vs. 2 (2.5) Nervous system disorders Akathisia 15 (9.5) vs. 10 (6.3) vs. 5 (6.3) Dizziness 6 (3.8) vs. 24 (15.1) vs. 1 (1.3) Drooling 13 (8.2) vs. 4 (2.5) vs. 1 (1.3) Headache 23 (14.6) vs. 19 (11.9) vs. 13 (16.3) Hypertonia 19 (12.0) vs. 6 (3.8) vs. 3 (3.8) Sedation 7 (4.4) vs. 17 (10.7) vs. 3 (3.8) Somnolence 18 (11.4) vs. 24 (15.1) vs. 2 (2.5) Tremor 31 (19.6) vs. 12 (7.5) vs. 12 (15.0) Psychiatric disorders Agitation 7 (4.4) vs. 5 (3.1) vs. 4 (5.0) Depressed mood 4 (2.5) vs. 0 (0) vs. 4 (5.0) Insomnia 19 (12.0) vs. 16 (10.1) vs. 12 (15.0) Schizophrenia 9 (5.7) vs. 14 (8.8) vs. 10 (12.5)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Canive, 2006 DB, RCT, crossover	NR	Withdrawals: 6 Withdrawals due to adverse events: NR	
Canuso 2009 DB RCT India, Russia, the Ukraine, and the United States Inpatient	Paliperidone vs. quetiapine vs. placebo Change in LSM (SE) Simpson-Angus Scale total score –0.1 (0.2) vs. –0.4 (0.2) vs. 0.2 (0.3) AIMS total score –0.1 (0.2) vs. –0.2 (0.2) vs. –0.2(0.2) BAS, rating for global severity of akathisia, shifts from baseline n(%) Worsened 11 (7.1) vs. 6 (4.0) vs. 5 (6.5) Unchanged 130 (84.4) vs. 125 (83.3) vs. 62 (80.5) Improved 13 (8.4) vs. 19 (12.7) vs. 10 (13.0)	116 withdrawals 31 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Chan, 2007 DB, RCT, parallel, multicenter Inpatients	Nonpregnant, non-lactating; 18-65 yrs.; primary diagnosis of DSM-IV schizophrenia or schizoaffective disorder; hospitalized due to acute relapse; evidence of response to antipsychotic medication; PANSS total score of at least 60 and a minimum score of 4 on at least 2 of the 4 items of the PANSS positive subscale; patients taking long-acting neuroleptic could be included if time period of at least 1 treatment cycle plus 1 week had elapsed since last injection. Exclusion criteria: psychiatric disorder other than schizophrenia or schizoaffective disorder requiring pharmacotherapy; serious suicidal ideations; first episode of schizophrenia or schizoaffective disorder; clinically significant neurologic abnormality other than tardive dyskinesia or EPS; current diagnosis of psychoactive substance dependence or history of drug or alcohol abuse within 1 month of study start; any acute or unstable medical condition; treatment with an investigational drug within 4 weeks of start of placebo washout.	aripiprazole: 15 mg/day risperidone: 6 mg/day Duration: 4 weeks	3 day placebo washout	Benzodiazepines for anxiety or insomnia; intramuscular benzodiazepines for emerging agitation if deemed necessary by investigatory; anticholinergic drugs for EOS not permitted during washout but allowed for treatment of EPS during double-blind period if deemed necessary (dose of anticholinergic drug could not exceed an equivalent of 6 mg/day of benztropine)
Chiu, 2006 Prospective, RCT, open-label study to evaluate pancreatic beta-cell function	18-60 yrs; BMI 20-30 kg/m2; fasting glucose level of 110 mg/dL or less; no personal or family history of diabetes; DSM-IV diagnosis of schizophrenia Exclusion criteria: Axis I disorder except schizophrenia; current substance abuse; medical conditions that could confound glycoregulatory assessment, including diabetes mellitus and other endocrine diseases; severe cardiovascular, hepatic, or renal disease; malignancy; epilepsy; pregnancy	olanzapine: 10 mg/day risperidone: 2 mg/day Duration: 2 weeks	At least 3 days	Not allowed: medications (e.g., lithium, carbamazepine, valproic acid, propranolol, tricyclic antidepressant, SSRI) that may influence body weight, glucose/lipid metabolism, or drug disposition. Others: NR
Chowdhury, 1999	Schizophrenia by ICD10, aged 15–60 years; duration of illness > 6 months and received at least one full course of treatment with conventional antipsychotic drugs (either chlorpromazine, 600–800 mg daily, haloperidol or trifluoperazine in equivalent doses) without adequate response; patients intolerant to traditional neuroleptic drugs because of intractable neurological and non-neurological side-effects, necessitating withdrawal of drug or inadequate dosing	Clozapine initial dose 50 mg/d, increased by 50 mg to 150 mg/d by week 2. By week 3, dose range 250–300 mg/d. Risperidone 1mg twice daily starting dose, then 2 mg twice daily from day 2 onwards. After week 1, 6 mg daily up to maximum 8 mg/d Duration:16 weeks Mean maximum daily dose, clozapine, 343 mg daily; risperidone, 5.8 mg	7 days	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Chan, 2007 DB, RCT, parallel, multicenter Inpatients	PANSS, CGI-S, CGI Baseline, days 7, 14, 21, and 28	Mean age: 35 yrs Male: 54% Ethnicity: NR	Schizophrenia: 96% Schizoaffective: 4%	95/12/83
Chiu, 2006 Prospective, RCT, open-label study to evaluate pancreatic beta-cell function	Metabolic parameters using intravenous glucose tolerance test (baseline and endpoint), laboratory assays	Mean age (SD): 37.3 (8.3) yrs Male: 69% Taiwanese: 100%	No significant differences between treatment groups in weight, BMI, glucose, insulin, total cholesterol, triglyceride, HDL, LDL, and leptin	NR/NR/26
Chowdhury, 1999	PANSS scores total (positive, negative, general subscales) Treatment success rate (> 20% reduction from baseline on PANSS) total; positive; negative, general subscales	Mean age (SD): clozapine 30.3 (8.78) years risperidone 32.43 (9.79) years clozapine 73.3% male risperidone 76.7% male Ethnicity NR	Paranoid subtype, clozapine 56.67%; risperidone 60%; Other subtypes included hebephrenia, residual and undifferentiated	NR/72/60 clozapine: 30 risperidone: 30

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Chan, 2007 DB, RCT, parallel, multicenter Inpatients	83 analyzed	Both groups showed significant improvement in primary and secondary efficacy parameters (all P values < 0.001) Both treatments demonstrated rapid onset of efficacy with statistically significant effects from week 1 (P<0.001 for primary efficacy parameter; P<0.007 for all secondary efficacy parameters) Responders (defined as CGI-I score </= 2 or >/= 30% decrease from baseline in PANSS total score): aripiprazole 51% risperidone 68% No significant difference; P=0.126
Chiu, 2006 Prospective, RCT, open-label study to evaluate pancreatic beta-cell function	0/0/26	Risperidone group: weight, BMI, fasting glucose, fasting insulin, triglyceride, total cholesterol, HDL, LDL, and leptin did not change significantly Olanzapine group: weight, BMI, fasting glucose, fasting insulin, triglyceride, total cholesterol, HDL, LDL, and leptin did not change significantly No significant difference between groups for glucose disappearance rate or insulin sensitivity Insulin secretion decreased significantly in olanzapine group (P=0.004)
Chowdhury, 1999	14/3/NR	PANSS scores total (positive, negative, general subscales): Clozapine: (n= 30) 93.16 (SD 9.57) (22.0,SD 6.74;23.67,SD 6.46;47.53,SD 7.18)(n= 30) 92.97,SD 14.80 (21.67,SD 5.92;23.73,SD 8.66;47.57,SD 8.72) Risperidone: (n= 24) 50.0,SD 17.80 (10.08,SD 3.06;14.08,SD 6.66;25.83,SD 8.74)(n= 22) 50.45,SD 20.74 (10.04,SD 3.26;14.55,SD 8.33;25.86,SD 9.98) Treatment success rate (> 20% reduction from baseline on PANSS) total; positive; negative; general subscales: Clozapine: 80%;80%;73.33%;80%66.7%;66.7%;63.33%;66.7%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Chan, 2007 DB, RCT, parallel, multicenter Inpatients	Patient report to investigator questions	Experienced at least 1 treatment emergent AE: aripiprazole: 84%, risperidone: 79% (no statistical difference between groups) Adverse Events (aripiprazole vs. risperidone), all P values >0.05 between groups: Abdominal pain: 6% vs. 0% Abdominal pain, upper: 8% vs. 3% Constipation: 10% vs. 12% Diarrhea: 8% vs. 3% Nausea: 4% vs. 6% Toothache: 6% vs. 9% Vomiting: 10% vs. 3% Nasopharyngitis: 6% vs. 0% Akathisia: 2% vs. 12% Dizziness: 4% vs. 12% Extrapyramidal disorder: 12% vs. 24% Headache: 8% vs. 3% Agitation: 8% vs. 0% Anxiety: 2% vs. 6% Insomnia: 27% vs. 21% Psychotic disorders: 16% vs. 6% Both groups showed mild body weight gain with no statistical difference [mean (SD)] aripiprazole vs. risperidone: 0.9 (2.2) kg vs. 1.5 (2.5) kg >7% weight increase: 4% vs. 12%; P=0.221 Serum prolactin levels, change from baseline aripiprazole vs. risperidone: -9.0 (96.4) vs. 55.4 (42.3) mg/dL; P<0.001)
Chiu, 2006 Prospective, RCT, open-label study to evaluate pancreatic beta-cell function	N/A	NR
Chowdhury, 1999	NR	Clozapine: tachycardia 76.66%; hypersalivation 60%; sedation 60%; weight gain 43.33%; constipation 30%; leucocytosis 26.66%. (1 patient suffered an episode of seizure) Risperidone: constipation 50%; dry mouth 46.66%; weight gain 43.33%; akathisia 36.67%; insomnia 33.33%; tachycardia 30%; impotence 26.66%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Chan, 2007 DB, RCT, parallel, multicenter Inpatients	Overall EPS -related AEs lower in aripiprazole than risperidone group EPS: aripiprazole 12%, risperidone 24% Akathisia: aripiprazole 2%, risperidone 12% For relief of EPS, 25% of aripiprazole patients and 12% of 41% of risperidone patients used anticholinergics as concomitant medications	Total: 22 (26.5%) Due to adverse events: 7 (8.4%)	
Chiu, 2006 Prospective, RCT, open-label study to evaluate pancreatic beta-cell function	NR	0 withdrawals 0 due to AEs	
Chowdhury, 1999	NR	clozapine: 6/30 (20%) Due to AE: 4/30 (13.3%) risperidone: 8/30 (26.7%) Due to AE: 3/30 (10%)	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Chrzanowski et al., 2006 (Extension of Pigott 2003) RCT, open-label extension	(1) stable patients who had completed the acute phase, and (2) patients who met the protocol criteria for relapse and had completed at least 2 weeks of double-blind therapy.	aripiprazole (15–30 mg/day) or olanzapine (10–20 mg/day) 52 weeks	NA	Other antipsychotics, investigational agents, or participation in another study were not allowed.
Chue, 2005 DB, RCT, double-dummy, multicenter, parallel, noninferiority study	Inpatients or outpatients aged 18-65; DSM-IV diagnosis of schizophrenia; total PANSS score > 50; no clinically relevant abnormal biochemistry, hematology or urinalysis lab values; remained symptomatically stable as indicated by stable oral dose and stable CGI scores for last 4 wks of oral risperidone run-in period Exclusion criteria: Moderate or severe symptoms of tardive dyskinesia at study entry; history of neuroleptic malignant syndrome, known to be risperidone unresponsive; required mood stabilizers; had been treated with clozapine in 2 months prior to screening or depot antipsychotic within one treatment cycle of screening or antidepressant within 30 days of run-in period	Oral risperidone: 2-6 mg/day Long-acting risperidone: 25-75 mg every 2 weeks Duration: 12 weeks active treatment	2 week washout of antipsychotics other than risperidone; total of 8 weeks open-label run-in	Anticholinergic medication could be initiated for emergent or worsening movement disorders and propranolol could be initiated for emergent or worsening akathisia; medication prescribed for sleep could be continued if used before study entry, or temazepam, zopiclone, zolpidem or chloral hydrate could be initiated during the study; lorazepam or oxazepam could be given intermittently for agitation Concomitant psychotropic meds received during double-blind treatment included antiparkinsonians and sedatives (lorazepam, oxazepam, clonazepam and zopiclone)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Chrzanowski et al., 2006 (Extension of Pigott 2003) RCT, open-label extension	PANSS and CGI scales at weeks 8, 16, 28, and 52.	Mean age: 41.5 54% male 96% white 1% African American 2% Hispanic	Weight- mean 73.0 kg Age at time of 1st diagnosis 30.4 years	NR/NR/214
Chue, 2005 DB, RCT, double-dummy, multicenter, parallel, noninferiority study	PANSS (Weeks 8 and 12), CGI (every 2 weeks)	Mean age: 40.0 yrs Male: 64.7% White: 87.8% Black: 5.5% Asian: 2.5% Hispanic: 0.15% Other: 4.1%	Oral vs long-acting risperidone Schizophrenia type: paranoid: 60.7% vs 62.7% undifferentiated: 17.4% vs 17.9% residual: 15% vs 13.5% disorganized: 6.5% vs 5.0% catatonic: 0.6% vs 0.9%	NR/779 (run-in period)/642

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Chrzanowski et al., 2006 (Extension of Pigott 2003) RCT, open-label extension	67/8/214	PANSS Total scores of aripiprazole −21.8 and olanzapine −23.8 (p=0.606) Aripiprazole vs. Olanzapine Chronic, stable mean changes at 52 weeks PANSS Positive −0.41 vs. −0.86 PANSS Negative −1.89 vs. −2.01 CGI-S −1.89 vs. −2.01 At 52 weeks CGI-I 3.17 vs. 3.08 Acute psychosis mean changes at 52 weeks PANSS Positive -6.30 vs. -7.47 PANSS Negative -4.54 vs. -3.84 CGI-S -0.75 vs. -0.87 At 52 weeks CGI-I 2.98 vs. 2.89
Chue, 2005 DB, RCT, double-dummy, multicenter, parallel, noninferiority study	2 withdrawn before beginning DB treatment 541 analyzed for efficacy 640 analyzed for safety	Changes ± (SE) in PANSS at endpoint, oral risperidone vs. long-acting risperidone, 95%CI PANSS total: -6.3 ± (0.7) vs. -5.4 ± (0.7); -0.90, 2.78 Positive symptoms: -2.0 ± (0.3) vs. -1.7 ± (0.3); -0.34, 0.99 Negative symptoms: -1.6 ± (0.3) vs. -1.5 ± (0.3); -0.59, 0.82 Disorganized thoughts: -1.2 ± (0.2) vs. -1.1 ± (0.2); -0.34, 0.71 Uncontrolled hostility/excitement: -0.4 ± (0.1) vs. -0.3 ± (0.1); -0.22, 0.43 Anxiety/depression: -1.0 ± (0.2) vs. -0.9 ± (0.2); -0.25, 0.57 CGI scores improved in both treatment groups; percentage of patients rated as not ill or with mild illness increased from 46.9% to 57.8% in oral risperidone group and from 49.2% to 57.9% in long-lasting risperidone group

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Chrzanowski et al., 2006 (Extension of Pigott 2003) RCT, open-label extension	Extrapyramidal symptom-related AEs the Simpson–Angus scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS)	Aripiprazole vs. Olanzapine n(%) Insomnia 24 (24) vs. 29 (26) Anxiety 10 (10) vs. 12 (11) Headache 9 (9) vs. 13 (12) Somnolence 9 (9) vs. 8 (7) Infection 7 (7) vs. 5 (5) Nervousness 6 (6) vs. 5 (5) Akathisia 5 (5) vs. 6 (5) Reaction schizophrenic 5 (5) vs.6 (5) Flu syndrome 4 (4) vs. 9 (8) CNS stimulation 4 (4) vs. 6 (5) Lightheadedness 3 (3) vs. 7 (6) Tremor 3 (3) vs. 7 (6) Extrapyramidal syndrome 3 (3) vs. 6 (5) Weight gain 0 vs. 6 (5)
Chue, 2005 DB, RCT, double-dummy, multicenter, parallel, noninferiority study	Patient reported, clinical lab tests (hematology, biochemistry, prolactin assay, urinalysis), vital signs, electrocardiogram, ESRS, VAS for pain	Oral risperidone vs. long-acting risperidone: Overall AEs: 59.9% vs. 61.1% Insomnia: 9.0% vs. 9.7% Anxiety: 7.2% vs.10.0% Headache: 7.2% vs. 8.2% Psychosis: 4.7% vs. 5.3% No significant changes in vital signs, electrocardiogram including QTc interval and lab values other than prolactin from baseline to endpoint; adverse effects potentially attributable to prolactin elevation reported in 2.5% of oral risperidone group and 1.3% of long0acting risperidone group No between-group differences or changes from baseline in ESRS total or cluster scores Pain at injection site was low (mean scores 18-20 on 100 point VAS scale) and comparable between placebo and risperidone

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Chrzanowski et al., 2006 (Extension of Pigott 2003) RCT, open-label extension	SAS (aripiprazole, −0.08; olanzapine-pine, −0.24; p=0.442), AIMS (aripiprazole, −0.42; olanzapine,−0.26; p=0.198), BARS (aripiprazole, −0.06;olanzapine, −0.13; p=0.176) EPS-related AEs Olanzapine 18 vs aripiprazole 10% Concomitant anticholinergic use for EPS aripiprazole, 22% vs. olanzapine,26%	66 withdrawals 8 due to AEs	
Chue, 2005 DB, RCT, double-dummy, multicenter, parallel, noninferiority study	No statistically significant difference between treatment groups at any timepoint on CGI dyskinesia, parkinsonism, or dystonia scales or in stage of parkinsonism	113 total withdrawals Withdrawals due to AEs: Oral vs long acting risperidone 4.7% vs 5.6%	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Ciudad, 2006 (Companion to Alvarez 2006) RCT, multicenter, open-label, parallel, flexible-dose study	Outpatient; 18-65 yrs; DSM-IV diagnosis of schizophrenia; baseline SANS global score >/= 10. Exclusion criteria: hospitalization in psychiatry department within 3 months prior to enrollment; treatment with either injectable depot antipsychotic within 2 weeks of enrollment, or clozapine, olanzapine, risperidone, or sertindole within previous month; severe risk of suicide or allergy; severe diseases other than schizophrenia requiring hospitalization within previous 3 months; glaucoma; history or presence of unclassified seizures, leucopenia or jaundice; pregnancy.	olanzapine: mean dose 12.2 mg/day risperidone: mean dose 4.9 mg/day Duration: 48 weeks randomized assessment	No washout period for previous antipsychotic and/or anticholinergic meds although overlapping during first month was allowed	Biperiden (up to 6 mg/day) to treat EPS symptoms but not as preventive measure; benzodiazepines/hypnotics up to 40 mg/day diazepam equivalent
Conley, 2001	Schizophrenia or Schizoaffective disorder by DSM-IV diagnosis, baseline PANSS score, 60–120, aged 18–64 years; out- or inpatients hospitalized ≤4 weeks	risperidone 2–6 mg/d (flexible dose); oral olanzapine 5–20 mg/d; oral Duration: 8 weeks Both drugs given once daily according to following regimens: days 1–2, 2 mg risperidone or 10 mg olanzapine; days 3–7, 2–4 mg risperidone or 5–10 mg olanzapine; days 8–14, 2–6 mg risperidone or 5–15 mg olanzapine; days 15–56, 2–6mg risperidone or 5–20 mg olanzapine	1 week gradual dis-continuation	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Ciudad, 2006 (Companion to Alvarez 2006) RCT, multicenter, open-label, parallel, flexible-dose study	SANS global score; SAPS; CGI-S; SFS-Spanish version, total and subscale scores Weeks 8, 24, and 48	Age: 36.5 yrs. Male: 72.3% Spanish: 100%	Body weight: Olanzapine: 73.6 kg Risperidone: 80.8 kg	NR/NR/250
Conley, 2001	Change scores: PANSS total; PANSS positive; PANSS negative; PANSS disorganized thoughts; PANSS uncontrolled hostility; PANSS anxiety/depression Response: ≥20% reduction in PANSS; 40% reduction in PANSS; CGI-I much or very much improved CGI-S Change scores: ESRS total, questionnaire, parkinsonism, akathisia, and dyskinesia	Mean age: risperidone 41.0 (11.0) years olanzapine 38.9 (10.5) years 72.7% male Ethnicity NR	79% were outpatients Schizophrenia (n= 325) or schizoaffective disorder (n= 52) Duration of illness: mean risperidone 16.5 (10.5) years, olanzapine 15.4 (10.6) years	NR/NR/377 risperidone 188 olanzapine 189

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Ciudad, 2006 (Companion to Alvarez 2006) RCT, multicenter, open-label, parallel, flexible-dose study	250 randomized; 3 terminated before receiving study meds; 12 had no post-baseline efficacy data Safety analysis: 247 Efficacy analysis: 235	Significant within-group SFS total score improvements seen in both treatment groups (P=0.0006) In olanzapine group, significant improvements also seen in social engagement/withdrawal (P<0.0001), interpersonal communication (P<0.0001), independence (performance, P=0.0014), and independence (competence, P<0.0001) scores In risperidone group, significant improvements observed for social engagement/withdrawal (P=0.0284) and interpersonal communication (P<0.0001); significant worsening seen in occupation/employment category (P=0.0092) Olanzapine patients showed greater improvement over baseline in SFS total score and all SFS domains compared to risperidone patients, with significant between-group differences on the SFS total score and all SFS domains except interpersonal communication and prosocial activities; greatest intergroup divergence in SFS-related endpoints was occupation/employment domain (P=0.0024) Visit-wise comparisons showed significant differences of olanzapine over risperidone in SFS total score at all visits. Reduction in effectiveness measures from baseline, mean change (SD) olanzapine vs. risperidone: SANS global: 5.93 (0.4) vs. 4.53 (0.4), P=0.0151 SANS total: 32.9 (2.3) vs. 24.97 (2.4), P=0.0168 SANS composite: 26.65 (2.0) vs. 20.45, P=0.0183 SAPS global: 3.31 (0.3) vs. 2.41 (0.3), P=0.0207 SAPS total: 18.98 (1.5) vs. 13.65 (1.6), P=0.0116 SAPS composite: 15.66 (1.2) vs. 11.25 (1.3), P=0.0115 CGI-S: 1.0 (1.0) vs. 0.6 (1.1), P=0.0082 Higher proportion of olanzapine subjects showed clinical response : 69.2% vs. 48.7%, P=0.0014
Conley, 2001	Risperidone 53/NR/188 olanzapine 43/NR/189	Change scores: PANSS total; PANSS positive; PANSS negative; PANSS disorganized thoughts; PANSS uncontrolled hostility; PANSS anxiety/depression: Risperidone: (n= 134) –16.0 (16.6);–5.6 (6.4);–3.5 (6.0);–2.9 (4.6);–1.4 (2.8);–2.5 (3.6) Olanzapine: (n= 144) –15.4 (16.8);–4.8 (6.4);–3.3 (5.7);–3.5 (4.7);–1.7 (2.7);–2.2 (3.4) Response: ≥20% reduction in PANSS; 40% reduction in PANSS; CGI-I much or very much improved: Risperidone: 69/188;34/188;60/188(data not available for all participants) Olanzapine: 68/189;23/189;58/189 (data not available for all participants) CGI-S: Risperidone: (n= 133) not ill/very mild/mild n= 67, moderate/marked n= 62, severe/extremely severe n= 4 Olanzapine: (n= 145) not ill/very mild/mild n= 69, moderate/marked n= 75, severe/extremely severe n= 1 Change scores: ESRS total, questionnaire, parkinsonism, akathisia, and dyskinesia: Risperidone: (n= 133) –1.3 (4.6);–0.6 (2.4);–0.8 (3.4);–0.2 (1.0);–0.4 (2.4) Olanzapine: (n= 145) –1.6 (4.1);–0.5(2.4);–1.0 (3.3);–0.2 (0.8);–0.5 (2.2)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Ciudad, 2006 (Companion to Alvarez 2006) RCT, multicenter, open-label, parallel, flexible-dose study	NR	Most Frequent Adverse Events (drug groups combined) : anxiety: 13% insomnia: 10.1% tremor: 9.7% Adverse Events (olanzapine vs. risperidone): tremor: 5.6% vs. 13.8%; P=0.0301 akathisia: 1.6% vs. 8.9%; P=0.0099 sexual dysfunction: 0.8% vs. 5.7%; P=0.0357 weight gain: 3.8kg [SD=6.1] vs. 2.1 kg [SD=6.0]; P=0.5467 >7% weight increase: 40.7% vs. 17.3%; P=0.0012
Conley, 2001	Change scores: ESRS total, questionnaire, parkinsonism, akathisia, and dyskinesia	All risperidone versus olanzapine Serious adverse events: 15/188 versus 22/189; psychosis: 8/188 versus 8/189; suicide attempt: 2/188 versus 5/189; agitation: 3/188 versus 3/189; depression: 3/188 versus 3/189; insomnia: 3/188 versus 2/189; hallucinations: 2 versus 3; drug abuse: 0 versus 3; cardiovascular symptoms: 0 versus 3; gastrointestinal disorders: 0 versus 3; other: 14 versus 21 Weight gain: 3.4 lb (SD 7.8) versus 7.2 lb (SD 11.2); increase in body weight of 7%: 18/155 versus 44/161 Less serious adverse events: somnolence: 69/188 versus 73/189; insomnia: 45 versus 35; headache: 41 versus 32; agitation: 29 versus 40; dry mouth: 21 versus 42; rhinitis: 30 versus 31; dizziness: 26 versus 27; anxiety: 20 versus 23; vision abnormalities: 12 versus 19

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Ciudad, 2006 (Companion to Alvarez 2006) RCT, multicenter, open-label, parallel, flexible-dose study	NR for olanzapine vs. risperidone	Total withdrawals: 72 (30.6%) Withdrawals due to AEs: 10 (4.3%)	
Conley, 2001	Extrapyramidal symptoms: 45/188 versus 38/189. Patients using antiparkinsonian medication: 61/188 versus 53/189 Outcome: change scores: ESRS total, questionnaire, parkinsonism, akathisia, and dyskinesia Risperidone: (n = 133) –1.3 (4.6); –0.6 (2.4); –0.8 (3.4); –0.2 (1.0); –0.4 (2.4) Olanzapine: (n = 145) –1.6 (4.1); –0.5 (2.4); –1.0 (3.3); –0.2 (0.8); –0.5 (2.2)	Risperidone 53/188 (28.2%) Due to AE 22/188 (11.7%) Olanzapine 43/189 (22.8%) Due to AE 17/189 (8.99%)	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Conley, 2003 Kelly, 2003 DB, crossover Inpatients Funding: NIHM grant	Schizophrenia	olanzapine: 50 mg/d, and clozapine: 450 mg/day, each for 8 weeks	1 week washout of conventional antipsychotics	NR
Conley, 2005 RCT, parallel, DB X 12 weeks Inpatients - treatment resistant	Between 18 - 65 years who met DSM-IV criteria for schizophrenia, and were treatment resistance: (definition: persistent positive psychotic symptoms at study entry "moderate" severity (≥ 4 points on a 1-7 point scale) on 2 of 4 psychosis items on the BPRS; persistent global illness severity (BPRS ≥45 points on the 18-item scale and a CGI score of ≥4 points; 2 prior failed treatment trials with 2 different antipsychotic at doses of at least 600mg/day chlorpromazine equivalents, each of at least 6 weeks duration; and no stable period of good social/occupational functioning within the previous 5 years).	Risperidone 3-5mg/day (Mean 4.31± 0.63 mg/day), Quetiapine 300 mg to 500 mg/day (Mean 463.6 ± 50.5 mg/day); Fluphenazine 10-15 mg/day (Mean 13.2 ±1.17 mg/day (flexible dosing to target doses during the initial week of therapy)	Prior to randomization, subjects were given a 4-6 week, open-label trial with either olanzapine or a typical antidepressant other than fluphenazine. Dose was chosen by clinician. Pts who did not achieve a 20% reduction in BPRS scores and had a total BPRS ≥35 points and a CGI score ≥4 points were randomized.	up to 10mg/day of lorazepam prn; benztropine (up to 4mg/day) and propranolol 30-120mg/day if experiencing EPS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Conley, 2003 Kelly, 2003 DB, crossover Inpatients Funding: NIHM grant	Weekly rating of Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impression Severity Scale (CGI-S)	Mean age: 38 years	100% inpatients	NR/NR/13
Conley, 2005 RCT, parallel, DB X 12 weeks Inpatients - treatment resistant	BPRS and CGI ratings performed weekly. Simpson Angus Scale (SAS), the Barnes Akathisia Scale, Assessment of Involuntary Movements Scale. Quality of Life Scale at BL and end point. (Changes in Sexual Functioning Questionnaire, the Prolactin-Related Adverse Event Questionnaire, the Nurses Observation Scale for Inpatient Evaluation, the Overt Aggression Scale, laboratory and metabolic measures, and a 15-test battery of neuropsychological testing were obtained but not reported)	Mean age: 44.3±7.6 Male: 85% African-American: 58% Ethnicity: NR	During lead-in phase, 12 (23%) were treated with olanzapine and 40 (77%) with conventional antipsychotics. Mean chlorpromazine dosing equivalents were 724.3 ± 564.6 mg/day for those treated with conventional antipsychotics (n=40) and 18.2 ± 6.0 mg/day for those treated with olanzapine (n=12). Positive Psychopathology Rating: Significant time effect for all groups: p=0.05; no drug-by time effect	NR/52/40

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Conley, 2003 Kelly, 2003 DB, crossover Inpatients Funding: NIHM grant	NR/NR/13	Change scores from baseline: clozapine vs olanzapine: Total BPRS: C: -6.5 vs O: -1.0 Positive: C: -1.7 vs O: -0.5 Negative: C: +0.5 vs O: +1.3 Activation: C: -1.7 vs O: -0.6 Anxiety/depression: C: -2.5 vs O: -1.6 Hostility: C: -1.1 vs O: -0.1 CGI-S: C: -0.3 vs O: +0.1 Laboratory Values: Baseline fasting blood glucose (mg/dL): O: 94.6 + 14.4; C: 92.8 +10.2 Change in fasting blood glucose (mg/dL): O: 3.4 + 27.8; C: 10.8 + 2.9 Baseline total cholesterol (mg/dL): O: 198.0 + 44.0; C: 209.6 + 28.6 Change in total cholesterol (mg/dL): O: 4.3 + 35.6; C: 37.6 + 41.2 Baseline serum triglycerides (mg/dL): O: 141.4 + 40.4; C: 181.0 + 146.2 Change in serum triglycerides (mg/dL): O: 6.6 + 33.1; C: 162.8 + 258.1 Baseline alanine aminotransferase (ALT) (IU/L): O: 42.4 + 49.8; C: 22.0 + 13.5 Change in alanine aminotransferase (ALT) (IU/L): O: -12.3 + 28.2; C: 14.6 + 20.0 Baseline aspartate aminotransferase (AST) (IU/L): O: 23.7 + 15.9; C: 18.0 + 5.1 Change in aspartate aminotransferase (AST) (IU/L): O: -3.6 + 7.0; C: 10.4 + 11.5 Baseline lactate dehydrogenase (LDH) (IU/L): O: 153.4 + 45.5; C: 128.6 + 6.7 Change in lactate dehydrogenase (LDH) (IU/L): O: -1.6 + 41.3; C: 88.2 + 125.5
Conley, 2005 RCT, parallel, DB X 12 weeks Inpatients - treatment resistant	NR/2/38	Discontinuation Rate: NS Psychopathology Ratings: BL to Endpoint Total BPRS score: ≥ 20% decrease noted in 23% of R subjects, 25% quetiapine subjects, and 15% fluphenazine-treated subjects; p=0.89 CGI severity score: No change Positive: (final change score: R: 1.77 ±1.31; Q: 0.67 ± 1.02, F: 0.92 ± 0.93 ;combined, p=0.05) Negative: (final change score: R: -0.15 points; Q: 0.42 points, F: -0.23 points, p=0.01). Significant time-by-drug interactions was noted driven primarily by fluphenazine during wks 1-11 Anxiety/depression-(final change score: R: -1.15 ±5.91, Q: -1.33 ± 3.70, F:-1.08 ± 5.20; p=NS Hostility: p=NS Activation: p=NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Conley, 2003 Kelly, 2003 DB, crossover Inpatients Funding: NIHM grant	Patient self-report	Dry mouth: O: 8(80%), C: 2(20%) Blurry vision: O: 4(40%), C: 0 Urinary hesitancy: O: 0, C: 1(10%) Constipation: O: 6(60%), C:1(10%)0 Tachycardia: O: 2(20%), C: 0 Diarrhea: O: 3(30%), C: 0 Nausea: O: 9(90%), C: 6(60%) Dyspepsia: O: 3(30%), C: 7(70%) Headache: O: 6(60%), C: 4(40%) Somnolence: O: 10(100%), C:10(10%) Lethargy: O: 6(60%), C: 9(90%) Myoclonus: O: 1(10%), C: 3(30%) Stuttering: O: 0, C: 2(20%) Sialorrhea: O: 1(10%), C: 8(80%) Sweating: O: 1(10%), C: 5(50%) Urinary frequency: O: 1(10%), C: 4(40%) Dysphagia: O: 0, C: 2(20%) Orthostasis: O: 3(30%), C: 1(10%) Dizziness: O: 6(60%), C: 6(60%) Increased appetite: O: 4(40%), C: 5(50%)
Conley, 2005 RCT, parallel, DB X 12 weeks Inpatients - treatment resistant	Simpson Angus Scale for EPS Quality of Life Scale for items relevant to inpatients	"No significant differences in side effects noted among the groups" R (n=13) vs. Q (n=12); F (n=12) Dry mouth: 15%, 33%, 17% Blurry vision: 15%, 17%, 17% Urinary hesitancy: 0, 17%, 17% Constipation: 0, 17%, 17% Diarrhea: 15%, 17%, 0 Nausea: 23%, 8%, 17% Dyspepsia: 7%, 8%, 23% Headache: 54%, 42%, 42% Somnolence: 38%, 25%), 33% Lethargy: 31%, 17%, 25% Insomnia: 23%, 25%, 42% Anxiety: 15%, 8%, 8% Urinary frequency: 8%, 8%, 0 Increased appetite: 23%, 35%, 17% Dizziness: 23%, 8%, 8% Orthostasis:38%, 8%, 17% Weight reduction at endpoint:: R: -0.65 ±2.43 kg; Q: -1.2 ± 11.22 kg; F: -2.6 ± 5.7 kg; p=NS Quality of Life Interview at Endpoint: How do you feel about your life in general (endpoint compared to BL): R (+0.9), Q: (+0.1), F-(-0.9) Endpoint: Mean rating for all questions: R: 4.73 (mostly satisfied), Q: 4.65 (mostly satisfied), and F: 4.07 (mixed); p=NS

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Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Conley, 2003 Kelly, 2003 DB, crossover Inpatients Funding: NIHM grant	SAS scores decreased by 1.3 clozapine increased 0.3 olanzapine Akathisia 20% clozapine 20% olanzapine 1 subject received benztropine while on olanzapine	6 withdrawals 1 withdrawal due to adverse events	
Conley, 2005 RCT, parallel, DB X 12 weeks Inpatients - treatment resistant	"No significant differences among the group with all 3 groups showing improvements" Benztropine was given to 36%, 17%, 30% of F, R and Q -treated pts; p=NS Propranolol was given to 1 pts in each of the drug groups lorazepam was given to 82%, 75%, 70% of F, R, and Q pts; p=NS SAS: Q: all improved -1.64 points, R: -1.3 points; F: -0.69 points; p=NS	18 total withdrawals 2 due to AEs (both on quetiapine-1-abnormal EKG, 1-tremor)	Doses were increased in 39%, 58%, and 31% for R, Q, F respectively. Doses were lowered in 1 subject each on F and R. QoL Interview: The risperidone group had the lowest ratings at baseline, and no significant differences were noted after controlling for it.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Cutler, 2008 DB RCT 35 centers United States and 9 in India.	Men and women aged 18 to 65 years, a body mass index between 18 and 35 kg/m2, schizophrenia, CGI-S or 4 or more , PANSS > 70 and rating of 4 (moderate) or greater on at least 2 of PANSS Positive symptoms: delusions, conceptual disorganization, hallucinations, and suspiciousness/ persecution .	3 weeks - Iloperidone 24 mg n=295 Ziprasidone 160 mg n=149 placebo n=149.	1 week titration period	Zolpidem (or similar medication) and Benztropine
Daniel, 1996 Crossover	Patients with chronic schizophrenia or schizoaffective disorder, with treatment failures or intolerant to conventional antipsychotic side effects	clozapine or risperidone; dose titrated by clinician x 6 weeks. Dose was held stable during weeks 5 & 6. mean clozapine dose: 375mg/d (range 75-800mg) mean risperidone dose: 6.1mg/d (range 1-10mg)	7 days	estazolam, lorazepam for insomnia, lorazepam for agitation, benztropine for EPS. Other psychoactive drugs continued, but no dose changes allowed. Drugs used: valproic acid, fluoxetine, paroxetine, sertraline, clonazepam, and clorazepate
Davidson, 2007 RCT, DB, PCT, parallel, multicenter (international sites)	Male & female ≥ 18 years of age and experiencing an acute episode of schizophrenia, as represented by a PANSS total score between 70 and 120. Must have been diagnosed with schizophrenia according to DSM-IV criteria for at least 1 year prior to screening and have agreed to voluntary hospitalization for a minimum of 14 days.	Paliperidone ER (3mg, 9mg, and 15mg) as once daily dosing compared with Placebo or Olanzapine 10mg/day in a 6-week study.	5-days screening, patients discontinued prior medications for 3 days prior to randomization (antipsychotic medication, antiparkinsonian drugs, beta-blockers, and prescription herbal, or over the counter psychotropics.	Benzodiazepines were permitted with a stable dose for at least 3 months. Benztropine 1 or 2mg twice daily or biperiden 2mg 3 times daily were permitted for movement disorder treatment.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Cutler, 2008 DB RCT 35 centers United States and 9 in India.	Assessed at baseline, daily during titration and on days 10, 14, 21, and 28 PANSS, BPRS, CGI-S	Age 39.9 yrs 79.6% male 35.1% white 50.4% black 8.8% Asian 0.5% American Indian 0.3% Pacific Islander 4.9% other	Diagnosis Schizophrenia, disorganized 3.9% Schizophrenia, paranoid 84.5% Schizophrenia, undifferentiated 11.6%	913/ NR / 593
Daniel, 1996 Crossover	Blinded rating of Symptoms by the PANSS, Severity of illness by the CGI severity subscale, Cognition by: IQ, Wechsler Memory Scale, Semantic Fluency, the Boston Naming test, Rey Figure, Facial Recognition, the Continuous Performance Test, and the Wisconsin Card Sorting Test. Tests completed weekly	Mean age 33.8 years (22-51) 35% male ethnicity NR	Mean age at onset: 22.7 (15-32) mean # prior hospitalizations: 3.9 (1-10) mean # prior antipsychotic trials: 4.3 (2-8) 95% outpatients	NR/NR/20 enrolled
Davidson, 2007 RCT, DB, PCT, parallel, multicenter (international sites)	Primary efficacy endpoint - PANSS total score from base line to end point Secondary efficacy endpoint - CGI-S scores from base line to end point and in PSP scale in patients functioning in four areas from base line to end point PANSS Marder factor scores from base line to end point	Mean age: 36.8 years 68.0% male 32.0% female 49.0% white 21.0% black/ African American 24% Asian 6% Other	Previous antipsychotic therapy atypical 59 conventional 55 PANSS total score 93.0 age at diagnosis 25.1 weight 75.2 Kg	732/NR/618

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Cutler, 2008 DB RCT 35 centers United States and 9 in India.	212 / 0 / 593	Iloperidone vs. Ziprasidone vs. Placebo Adjusted mean changes BPRS 7.39 (0.63)* vs.7.21 (0.89)* vs. 4.62 (0.91) PANSS-P 4.21 (0.34)*** vs. 4.23 (0.48)*** vs. 2.22 (0.49) PANSS-N 2.96 (0.27)* vs. 3.06 (0.38)* vs. 1.91 (0.39) PANSS-GP 4.94 (0.54) vs. 5.24 (0.76)vs. 3.18 (0.77) CGI-S 0.65 (0.05)** vs. 0.67 (0.08)* vs. 0.39 (0.08) *P < 0.05 (2-tailed) versus placebo **P < 0.01 (2-tailed) versus placebo ***P < 0.001 (2-tailed) versus placebo
Daniel, 1996 Crossover	3 withdrawn (during risperidone treatment): 1 due to adverse events, 1 due to adverse events and lack of effect, 1 withdrew after achieving satisfactory response, in order to obtain non-study drug 17 analyzed	No significant difference on PANSS total, positive or negative subscales, or CGI (data not reported). No significant differences on cognitive tests (after application of Bonferroni adjustment for multiple comparisons)
Davidson, 2007 RCT, DB, PCT, parallel, multicenter (international sites)	253/6/605	Paliperidone ER = significant improvements in PANSS total and PANSS factor scores (p<0.05) and in personal and social functioning (p<0.001) compared with placebo. 59% completed 6-week study. PANSS total score in placebo vs. Paliperidone ER = -2.8±20.9, -15.0±19.6,-16.3±21.8 and -19.9±18.4, respectively. PANSS Marder factor shows paliperidone ER improvement over placebo (P≤0.005)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Cutler, 2008 DB RCT 35 centers United States and 9 in India.	Incidence of treatment emergent adverse events (TEAEs) and clinically meaningful changes from baseline in EPS (measured by ESRS and Barnes Akathisia Scale [BAS), vital signs including orthostatic changes in blood pressure and heart rate (HR), 12-lead electrocardiography measures, weight, and laboratory values.	Iloperidone vs. Ziprasidone vs. Placebo n(%) At least 1 AE 255 (85) vs. 130 (87) vs. 108 (74) Dizziness 51 (17) vs. 20 (13) vs. 11 (8) Sedation 38 (13) vs. 41 (27) vs. 12 (8) Weight increased 34 (11) vs. 7 (5) vs. 3 (2) Dry mouth 26 (9) vs. 11 (7) vs. 1 (0.7) HR increased 24 (8) vs. 9 (6) vs. 1 (0.7) Nasal congestion 25 (8) vs. 5 (3) vs. 4 (3) Tachycardia 28 (9) vs. 3 (2) vs. 1 (0.7) EPS 10 (3) vs. 14 (9) vs. 3 (2) Agitation 10 (3) vs. 10 (7) vs. 4 (3) Orthostatic hypotension 21 (7) vs. 0 vs. 3 (2) Somnolence 12 (4) vs. 9 (6) vs. 2 (1) Restlessness 11 (4) vs. 8 (5) vs. 3 (2) Anxiety 9 (3) vs. 8 (5) vs. 1 (0.7) Akathisia 4 (1) vs. 11 (7) vs. 0
Daniel, 1996 Crossover	Adverse events assessed by a self-administered multiple choice questionnaire on the severity of side effects of each drug (none, mild, moderate, severe) with respect to: insomnia, sleepiness, loss of appetite, restlessness, lack of alertness, nausea, inability to think clearly, memory problems, and inability to concentrate. A score of 0 to 3 was assigned to each response.	7/17 (41%) required Anti-EPS meds while on risperidone 0 required Anti-EPS meds while on clozapine Prior to Bonferroni adjustment: Sleepiness/lack of alertness: SS more with clozapine Restlessness/insomnia: SS more with risperidone Inability to think clearly/inability to concentrate: SS related to clozapine dose After correction: restlessness not significantly different no dose correlation apparent
Davidson, 2007 RCT, DB, PCT, parallel, multicenter (international sites)	Voluntary report of AE at every scheduled visit. Treatment emergent glucose-, prolactin-, and EPS- related AE's as defined by WHO AE terms. AIMS, BARS, SAS days 8-15 and every 7 days up to and including day 43. Clinical lab evaluations, ECG, vital signs, physical examination and assessment of bodyweight.	Study discontinuation similar in all groups (2-5%). TEAEs in all groups were insomnia, headache and tachycardia. Serious TEAEs were low in all treatment groups (placebo = 7%, paliperidone ER 3mg = 6%, paliperidone ER 9mg = 10%, paliperidone ER 15mg = 5%, and olanzapine = 6%) Most commonly reported TEAE as serious was psychosis (6% in placebo, 5% in paliperidone ER 3mg, 6% in paliperidone ER 9mg, 3% in paliperidone ER 15 and olanzapine groups). Glucose related AE's across all groups = n = 6 SAS = no statistically significant increase in paliperidone ER 3 mg and 15 mg groups compared to placebo. Increase in SAS global score for paliperidone ER 9 mg compared to placebo (p=0.004)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Cutler, 2008 DB RCT 35 centers United States and 9 in India.	Iloperidone vs. Ziprasidone vs. Placebo n(%) EPS 10 (3) vs. 14 (9) vs. 3 (2) Additional results presented graphically	212 total 40 due to AEs	
Daniel, 1996 Crossover	7/17 (41%) required Anti-EPS meds while on risperidone 0 required Anti-EPS meds while on clozapine	3/20 (15%) total withdrawals 2/20 (10%) due to AEs	Results not reported by first intervention/second intervention. Not possible to evaluate effect of order of assignment, although authors use Bonferroni adjustment to correct for this.
Davidson, 2007 RCT, DB, PCT, parallel, multicenter (international sites)	BARS = absent in 76-79% of patients in placebo, paliperidone ER 9mg and 15mg groups and 85% in paliperidone ER 3mg group. AIMS score reported as 0.0. Most movement disorder-related TEAEs = mild or moderate	253 total withdrawals 23 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Deberdt, 2008 DB RCT	Males and females between 18 and 75 years of age and diagnosed with schizophrenia or schizoaffective disorder according DSM-IV: a confirmed psychotic episode within the last 5 years prior to enrollment; clinically stable for at least 15 days on a fixed dose of olanzapine (10–20 mg/day) prior to enrollment; obese (body mass index [BMI] 30 kg/m2) or overweight (BMI 25 kg/m2 and 30 kg/m2) with at least one cardiovascular risk factor (diabetes mellitus or impaired fasting glucose, dyslipidemia, elevated blood pressure, or waist circumference 102 cm for men or 88 cm for women); free of any other signifi cant medical illness at enrollment.	Olanzapine group: continue with original olanzapine treatment, then 7.5-20 mg/day; Mean modal dose of 16.9 mg/day; 24 weeks Quetiapine griyo: olanzapine dose gradually decreased and completely discontinued by Day 7, with quetiapine dose gradually increased to 300-800 mg/day; mean modal dose of 439.7 mg/day; 24 weeks	None	concomitant medications with primary central nervous system activity were not allowed in this protocol.
Dollfus, 2005 DB, RCT	Age 18-65 pts with post-psychotic depression according to DSM-IV criteria with maximum PANSS score of 28 and minimum total MADRS score of 16 at screening and baseline	Olanzapine 5-15 mg/day Risperidone 4-8 mg/day	1 wk	benzodiazepines; biperidine
Feldman, 2003 Sutton, 2001 (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Negative symptoms in older patients	Subset of Tran - patients aged 50 to 65 years.	olanzapine 10-20mg/d risperidone 4-8mg/d Duration: 28 weeks mean dose for subset NR	NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Deberdt, 2008 DB RCT	PANSS; CGI-S; level of psychiatric care. Relapse was defined as the occurrence of at least 1 of the following 3 events: hospitalization due to psychiatric reasons; 20% worsening on the PANSS total score and an increase in the level of care for psychiatric reasons compared to baseline; 20% worsening of PANSS total score and worsening of CGI S by at least 1 level compared with baseline and CGI-S score of 4. PANSS and CGI-S were administered at every visit (visit 2 to visit 13). 12 visits during DB phase (3 visits 1 week apart, 2 visits 2 week apart and 7 visits 3 weeks apart)	Olanzapine vs Quetiapine Age (SD): 45.4 (9.4) vs 42.5 (11.5) years Gender: NR Ethnicity: NR	Olanzapine vs Quetiapine Mean time on olanzapine (SD) 67.5 (98.5) vs 69.4 (107.8) weeks; *P*=0.554 Mean total PANSS (SD): 61.1 (17.9) vs 65.9 (20.4); *P*= 0.033 Mean BMI (SD): 34.6 kg/m2 (7.1) vs 37.5 kg/m2 (8.6); *P*=0.042	NR/NR/133
Dollfus, 2005 DB, RCT	Change in MADRS from baseline; weekly assessments	Mean age: 39.3 yrs 69.7% male Ethnicity NR	Use of biperiden during study: 9% (7/76 enrolled pts)	NR/NR/76
Feldman, 2003 Sutton, 2001 (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Negative symptoms in older patients	PANSS total, positive, negative and general psychopathology subscale scores SANS composite and summary subscale scores CGI-S	Mean age: 57 92.3% white 56.4% male	82% schizophrenia diagnosis 64% had prominent negative symptoms mean # prior episodes: 10	NR/NR/39 19 olanzapine 20 risperidone

Evidence Table 1. Head-to-head trials in patients with schizophrenia

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Deberdt, 2008 DB RCT	57/NR/133	Olanzapine vs Quetiapine Hospitalization for psychiatric reasons after Visit 2: 1 (1.47%) vs 5 (7.69%); *P*=NS 20% worsening in PANSS Total score and increase in Level of Care for psychiatric reason after Visit 2: 0 vs 2 (3.08%); *P*=NS 20% worsening on the PANSS Total score 7 and worsening of CGI-S by at least one level compared to baseline and CGI-S score: 4(10.29%) vs 7 (10.77%); *P*=NS Patients meeting at least one of the above criteria: 8 (11.76%) vs 10 (15.38%); *P*=NS Discontinuations due to psychiatic AEs higher in quetiapine group (*P*=0.031) Improvements in PANSS total socres throughout study for both groups (shown in figure 3). At weeks 13 and 19, improvement from baseline was no longer significant for quetiapine group, and significantly worse than olanzapine group.
Dollfus, 2005 DB, RCT	NR/NR/76	Mean change from baseline in MADRS score at 8 wks: O -14.1 (SD 8.4) v R -14 (SD 8.8); p reported as not SS (no figure provided) Mean change from baseline in positive PANSS score at 8 wks (or at point of withdrawal) in pts with MADRS decrease of ≥30%: O -2 (SD 4.4) v R -2.9 (SD 3.4) Mean change from baseline in negative PANSS score at 8 wks (or at point of withdrawal) in pts with MADRS decrease of ≥30%: O -6.2 (SD 6.1) v R -6.2 (SD 5.4)
Feldman, 2003 Sutton, 2001 (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Negative symptoms in older patients	20/NR/39	At 8 weeks: Mean change in total PANSS: olanzapine 27.2, risperidone 21.0 (NS) Mean change in PANSS positive: olanzapine -6.8, risperidone -6.5 (NS) Mean change in PANSS General Psychopathology olanzapine: -10.8, risperidone: -10.0 (NS) Mean change PANSS negative: olanzapine: -8.8, risperidone: -4.9 (p = 0.032) Mean change SANS summary: olanzapine: -3.6, risperidone: -2.1 Mean change SANS composite olanzapine: -13.0, risperidone: -6.5 Mean change CGI-S olanzapine -0.8, risperidone: -0.7 At 28 weeks: Overall, change in scores decreased slightly Differences remained NS for all but PANSS negative (p=0.032) Differences on SANS remained NS for summary and composite scores Analysis of 5 components revealed SS on 2 items: Affective flattening: olanzapine: -5.2, risperidone -0.6 (p=0.033) Alogia olanzapine: -3.8, risperidone: -0.3 (p=0.007)

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Author, year study design	Method of adverse effects assessment	Adverse effects reported
Deberdt, 2008 DB RCT	Vital signs and weight, recording of adverse events, and review of treatment compliance at every visit. A physical examination, measurement of height and waist circumference. Laboratory tests (clinical chemistry, hematology, hepatitis, drug screen, pregnancy, TSH, prolactin, hemoglobin A1c, lipid panel, and insulin) were performed at Visit 1, and selected laboratory tests repeated throughout the study.	Weight gain higher in olanzapine group from weeks 2 to week 13 (*P*<0.05). No difference in weight gain at last visit. LOCF analysis showed no significant between group differences in weight (*P*=0.088), BMI (*P*=0.15), fasting glucose (*P*=0.228), HbA1c (*P*=0.318), cholesterol (*P*=0.471), LDL (*P*=0.981), HDL (*P*=0.872), Insulin (*P*=0.262) and triglycerides (*P*=0.167). No statistically significant differences in treatment-emergent AEs between treatment groups. Most common (≥5%) in the olanzapine treatment group were sedation, vomiting, anxiety, hypertension, insomnia, pharyngolaryngeal pain, somnolence, weight decrease, and weight increase. In the quetiapine treatment group,most common(≥5%) were sedation, anxiety, insomnia, weight increase, headache, constipation, dry mouth, auditory hallucination, paranoia, and agitation.
Dollfus, 2005 DB, RCT	NR	NR
Feldman, 2003 Sutton, 2001 (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Negative symptoms in older patients	See Tran 1997	% Olanzapine, % Risperidone, (p-value) Weight gain 25%, 0%, (p=0.047) Mean weight gain: 4.7kg, 0.6kg (p=0.052) With >20% incidence, but NS difference: somnolence 25%, 32% agitation 10%, 21% anxiety 30%, 5% (p=0.091) EPS: For measures of EPS, data for only 12 olanzapine and 9 risperidone available AIMS, BAS, and SAS NS difference, small changes

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Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Deberdt, 2008 DB RCT	NR	Olanzapine vs Quetiapine Total withdrawals: 20 vs 37 Withdrawals due to AEs: NR (total given in figure; 20-25%)	
Dollfus, 2005 DB, RCT	NR	NR / NR	Study did not enroll an adequate number of patients to achieve statistical significance (76 pts enrolled vs 160 intended sample size)
Feldman, 2003 Sutton, 2001 (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Negative symptoms in older patients	For measures of EPS, data for only 12 olanzapine and 9 risperidone available AIMS, BAS, and SAS NS difference, small changes	20 total withdrawals 6 due to adverse events	Small N; power for statistical differences lacking. Length of current episode: 120 days for risperidone patients, 61 days for olanzapine patients, but NS difference olanzapine: 70% male; risperidone: 42% male.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Fleischhacker, 2009 DB RCT Multinational -Australia, Europe, and South Africa Multicenter (119)	18 and 65 years of age, who were diagnosed with schizophrenia (according to the DSM-IV criteria) and were in acute relapse and who had demonstrated a previous response to antipsychotic drugs.	Olanzapine mean 15.4 mg/day n=348 Aripiprazole mean 23.0 mg/day n=355 6 week duration	2 day antipsychotic washout	Benzodiazepines and 4 mg/day lorazepam (or 20 mg/day diazepam) for anxiety plus 1–2 mg lorazepam (5–10 mg diazepam) if needed for sleep and anticholinergic drugs for extrapyramidal symptoms (EPS)
Garyfallos, 2003	50 acute ward patients fulfilling DSM IV criteria for schizophrenia, schizophreniform or schizoaffective disorder; at time of admission, they had not been on antipsychotic treatment	During stable period, mean doses: olanzapine: 18 mg/day (range: 10-20 mg/d) risperidone: 7.7 mg/day (range: 6-12 mg/d) 8-week study	No antipsychotics 1 month prior to hospitalization	Anticholinergic and lorazepam allowed if clinically indicated
Glick, 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use	see above	see above	none	Any required to treat patient and reduce risk of suicide. See results section for numbers of patients taking CPMs

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Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Fleischhacker, 2009 DB RCT Multinational -Australia, Europe, and South Africa Multicenter (119)	PANSS total and CGI-I and Clinical Global Impression Severity of Illness (CGI-S) at baseline and 6 weeks	Mean age olanzapine 37.3 aripiprazole 35.9 yrs % male olanzapine 56 aripiprazole 57 % white olanzapine 90 aripiprazole 92 % black olanzapine 5 aripiprazole 4 % other olanzapine 5 aripiprazole 5	Diagnosis olanzapine vs. aripiprazole Schizophrenia Type, n (%) Disorganized 28 (8) vs. 28 (8) Catatonic 1 (1) vs. 1 (1) Paranoid 272 (78) vs. 276 (78) Residual 4 (1) vs. 9 (3) Undifferentiated 43 (12) vs. 41 (12)	NR/NR/750
Garyfallos, 2003	PANSS evaluated at baseline and week 8	Mean age: NR 68% male Ethnicity: NR	NR	NR/NR/50
Glick, 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use	for CPMs, all relevant medications were recorded in case report forms and included in the clinical trial database. CPMs used after study drug randomization were identified and grouped into the following 4 classes: antipsychotics, antidepressants, sedatives/anxiolytics, and mood stabilizers. Once a CPM was assigned to a psychotropic class, all cases of use for that medication were included in the analysis. Stimulants, antidementia drugs, and analgesics were not considered for this analysis, as these are used for nonpsychiatric indications or for indications outside the scope of InterSePT (e.g., ADHD). Beta-blockers were excluded from the analysis except for propanolol.	see above	see above	see above

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Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Fleischhacker, 2009 DB RCT Multinational -Australia, Europe, and South Africa Multicenter (119)	181 / 0 / 703	Mean change in PANSS Total score olanzapine: -29.5 vs. aripiprazole: -24.6 Mean change in CGI-S olanzapine, 1.42; vs. aripiprazole, 1.25 Mean CGI-I score olanzapine, 2.23; vs. aripiprazole, 2.50 Responders olanzapine, 78%; vs. Aripiprazole 73%
Garyfallos, 2003	0/0/50	Mean change in PANSS totals score at endpoint: olanzapine: -26 vs risperidone: -32.7
Glick, 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use	NR/NR/NR	Patients who received at least 1 Concomitant Psychotropic Medication (CPM) / study duration: Clozapine: 92.4% vs olanzapine: 91.8% Mean number of CPM/patient: 3.8 (SD: 2.9) for clozapine vs 4.22 (SD: 3.16) for olanzapine Patients receiving CPM and least squares mean (LSM) daily dose, clozapine vs olanzapine: Antipsychotics: clozapine 85.6% vs olanzapine 81.7%, p = NR LSM daily dose:2.1mg (SD: 0.33 mg) vs 3.8mg (SD: 0.34mg), p<0.001 Antidepressants: clozapine 50.3% vs olanzapine 56.6%, p= NR LSM daily dose:16.7mg (SD: 1.05mg) vs 20.7mg (0.97mg), p<0.01 Sedative/anxiolytics: clozapine 59.3% vs olanzapine 66.0%, p = NR LSM daily dose:6.3mg (SD: 0.64mg) vs 10.1mg (0.61mg), p<0.001 Mood stabilizers: clozapine 25.0% vs olanzapine 30.2%, p = NR LSM daily dose: 487.3mg (SD: 43.2mg) vs 620.6mg (SD: 39.9mg), p<0.05 Daily dose of CPM in suicide attempters (ATs) and non-attempters (NATs): (Numbers of patients per group: ATs C=102, O=141; NATs: C=388, O=349 patients) Antipsychotics: for ATs: C: 2.7 vs O: 4.8, p=0.15; and for NATs: C: 2.1 vs O:3.8, p=0.001 Antidepressants: for ATs: C:20.7 vs O: 23.8, p=0.20; and for NATs: C: 15.6 vs O:19.3, p<0.01 Sedatives/anxiolytics: for ATs: C:8.9 vs O: 12.1, p<0.05; and for NATs: C: 5.7 vs O:9.6 p<0.001 Mood stabilizers: for ATs: C: 535.7 vs O; 656.2, p=0.26; and for NATs: C: 503.9 vs 624.9, p<0.05

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Fleischhacker, 2009 DB RCT Multinational -Australia, Europe, and South Africa Multicenter (119)	Adverse events (AEs) (either spontaneously reported or elicited during questioning), EPS via Simpson- Angus Scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale (AIMS)	Significant weight gain at Week 26 - olanzapine 40%vs. aripiprazole 21%; p < .05 Mean weight gain at Week 26 - olanzapine 4.30 kg vs. aripiprazole 0.13 kg Olanzapine vs. aripiprazole - n (%) Weight Gain 73 (21) vs. 21 (6) Insomnia 71 (21) vs. 95 (27) Anxiety 45 (13) vs. 56 (16) Somnolence 37 (11) vs. 15 (4) Asthenia 32 (9) vs. 27 (8) Headache 28 (8) vs. 54 (15) Reaction Schizophrenic 24 (7) vs. 32 (9) Akathisia 21 (6) vs. 33 (9) Dry mouth 20 (6) vs. 10 (3) Agitation 18 (5) vs. 23 (7) Nausea 12 (3) vs. 30 (9) Tremor 11 (3) vs. 21 (6) Vomiting 10 (3) vs. 23 (7) Psychosocial Support 8 (2) vs. 21 (6) Extrapyramidal Syndrome 4 (1) vs. 20 (6)
Garyfallos, 2003	Weight, BMI, triglycerides, and total cholesterol were measured at both baseline and week 8	Mean change (SD) at endpoint, olanzapine vs risperidone: Weight Change: +4.2 (2.6) vs +2.0 (0.7), p<0.001 BMI Change: +1.4 (0.8) vs +0.7(0.3), p<0.001 Triglycerides: +43.5 (26.9) vs +7.5 (20.1), p<0.001 Cholesterol: +10.2 (23.1) vs + 0.7 (16.4) , p=NS
Glick, 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use	NR in this paper, for general InterSePT, see above	NR in this paper, for general InterSePT, see above

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Fleischhacker, 2009 DB RCT Multinational -Australia, Europe, and South Africa Multicenter (119)	Mean change at Week 52 Simpson-Angus Scale Total score olanzapine 1.2 vs. aripiprazole .7 (p < .001; LOCF analysis). Barnes Akathisia Global Clinical Assessment score olanzapine .10 vs. aripiprazole no change (p = .043; LOCF analysis). EPS related AEs olanzapine 44 (13%) vs. aripiprazole 73 (21%)	181 withdrawals 55 due to AEs	
Garyfallos, 2003	NR	NR / NR	
Glick, 2004 Subanalysis of InterSePT showing patterns of concomitant psychotropic medication (CPM) use	NR in this paper, for general InterSePT, see above	NR in this paper, for general InterSePT, see above	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Guerje, 1998 Thomas, 1998	Diagnosis: schizophrenia, schizophreniform or schizoaffective disorders; Min score of 36 on BPRS as extracted from PANSS (items scored 1-7)	olanzapine 10-20mg/d risperidone 4-8mg/d Duration: 30 weeks	No longer than 9 days	NR
Harvey 2006 (Companion to Zhong 2006) DB, RCT Inpatients for 1st week then outpatients	Male and female; 18–65 years of age; a diagnosis of DSM-IV schizophrenia, a baseline PANSS score of ≥60, a CGI severity rating ≥4, and a score of ≥4 on one of the following PANSS positive symptom subscale items: delusions, conceptual disorganization, hallucinatory behavior, or suspiciousness/persecution; stable laboratory and electrocardiogram (ECG) results and to have a negative urine drug screen at study entry.	Quetiapine 400 mg Risperidone 4 mg 8 weeks	NR	Sleep medication and benzodiazepines were allowed as needed but were not allowed within 24 hours of clinical or neuropsychological assessments
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT, multicenter (US, Austria, Israel, Norway, Poland and The Netherlands)	Patients > 60 yrs with schizophrenia or schizoaffective disorder. PANSS scores 50-120 at baseline. Inpatient, outpatient, nursing home, board and care patients.	olanzapine: flexible dose 5-20mg/d mean modal dose: 11.46mg risperidone 1-3mg/d mean modal dose: 1..95mg Duration: 8-weeks	1-week washout	unclear
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT, multicenter (US)	Schizophrenia or schizoaffective disorder; baseline PANSS score 60-120; age 18-64 yrs; inpatient or outpatient (hospitalized </= 4wks at screening); not refractory to treatment with olanzapine or risperidone).	olanzapine 5-20mg/d risperidone 2-6mg/d once daily dosing titration unclear Duration: 8 weeks	1 week	not specified

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Guerje, 1998 Thomas, 1998	BPRS total score at week 22 through 30 Reduction of ≥ 20% PANSS total score at week 30 SF-36 and disease-specific Quality of Life in Schizophrenia scale at week 30	Mean age 35 - 36 58% male 89% Caucasian	Duration of Hospitalization prior 12 months: means 12 to 19 days Baseline PANSS means 89 to 95 Baseline BPRS: means 32 to 35	NR/NR/65 olanzapine = 21 risperidone = 21 haloperidol = 23
Harvey 2006 (Companion to Zhong 2006) DB, RCT Inpatients for 1st week then outpatients	At baseline and day 56 the following were measured- Social Skills Performance Assessment; The Penn Emotional Acuity Test; Two different versions of the Continuous Performance Test of vigilance; Part A and B of the Trail Making Test; Rey Auditory Verbal Learning Test, category and letter fluency	Mean age- 40 yrs 77% male 50% Caucasian 41% African-American 8% Hispanic 2% Asian		NR/ NR/673 of which 289 had valid assessments
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT, multicenter (US, Austria, Israel, Norway, Poland and The Netherlands)	Attention: Continuous Performance Test (CPT), Trail Making Test Part A (TMT) Memory: Serial Verbal Learning Test (SVLT) Executive Function: WCST, TMT part B Verbal fluency: category and phonologic fluency tests Measured at baseline, 4 and 8 wks, or at early termination Tests translated into local language PANSS weekly HAM-D, BQoL, and MMSE at baseline and endpoint	Mean age 71 36% male 60% white	N Prior Admits: 5.65 mean total PANSS score: 77 mean MMSE: 25 mean BQoL: 4.66 mean HAM-D: 7.66 mean ESRS: 11.4	NR/NR/176 79 olanzapine 74 risperidone
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT, multicenter (US)	PANSS scores at wks 0, 2, 4, 6 and 8 Cognitive tests: California Verbal learning Continuous performance test Spatial working memory Verbal fluency exam Trail-making test - parts A and B Wisconsin card-scoring test Given at baseline and 8 wks Because tests have multiple dependent measures, only parts of each test were collected at the sites and forwarded for analysis. Variables analyzed were selected by a consensus of "experts in neuropsychology and clinical trials"	Mean age 40 73% male Ethnicity NR	Mean # prior hospitalizations: 6.3 Mean Total PANSS score: 81	NR/NR/377* 189 olanzapine 188 risperidone *an unknown number of patients were enrolled at 2 additional sites, whose data were removed after it was deemed low quality."

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Guerje, 1998 Thomas, 1998	36/0/62	Compared with risperidone-treated patients, olanzapine-treated patients showed greater reduction in PANSS total (and PANSS psychopathology, and BPRS total score. Greater proportion also achieved reduction of 20% or more on PANSS total score at week 30. At week 30, olanzapine-treated patients had better profile of quality of life (SF-36 and disease-specific Quality of Life in Schizophrenia scale)
Harvey 2006 (Companion to Zhong 2006) DB, RCT Inpatients for 1st week then outpatients	NR/NR.NR	There were no overall differences between the treatments in their impact on social competence and neuropsychological performance. Change from baseline (SD) risperidone vs. quetiapine PANSS Total 21.53 (19.22) vs.22.52 (22.10) P = 0.68 Negative subscore 4.76 (5.69) vs. 5.37 (5.69) P = 0.41 Positive subscore 6.83 (5.82) vs. 6.69 (5.80) P = 0.85
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT, multicenter (US, Austria, Israel, Norway, Poland and The Netherlands)	67/NR/153 55 olanzapine 54 risperidone	Attention: SS change from baseline in both groups on TMT-A, not CPT NS difference between groups Memory: SS change from baseline in both groups on both tests NS difference between groups Executive domain: olanzapine: NS change from baseline on any test risperidone: SS change from baseline on TMT-B, WCST total errors, and verbal fluency NS difference between groups Analysis of categories of improvement (markedly, substantially, slightly or not improved) NS difference between drugs on any test except TMT-A: olanzapine SS > substantial or markedly improved, AND SS> not improved MANCOVA analysis of change in scores from baseline as function of medication: NS differences between groups MANCOVA analysis of completer/non-completer status and endpoint scores: NS differences between groups
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT, multicenter (US)	96/11/n varied by test and time-point (range 258-363)	Overall: SS changes from baseline for each drug on all measures except category fluency and SWMT (5-s delay). After Bonferroni adjustment, CVLT delayed recognition showed NS difference to baseline. Olanzapine vs Risperidone: NS difference on any variable Treatment x time effects: WCST total errors: risperidone > olanzapine (p = 0.042), BUT NS after Bonferroni adjustment. Stratification by improvements of 0.5 or 1.0 SD : NS difference between drug 40% improved by 0.5 SD 15% improved by 1.0 SD Anticholinergic med effects: NS Analyses of effect of smoking status and dose: NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Guerje, 1998 Thomas, 1998	Spontaneous reporting and BAS and SAS scales for EPS.	Trend for olanzapine-treated patients to evidence fewer treatment-emergent adverse effects
Harvey 2006 (Companion to Zhong 2006) DB, RCT Inpatients for 1st week then outpatients	NR	NR
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT, multicenter (US, Austria, Israel, Norway, Poland and The Netherlands)	ESRS at baseline and endpoint (wk 8)	NR
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT, multicenter (US)	ESRS at wks 0, 2, 4, 6 and 8	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Guerje, 1998 Thomas, 1998	No differences found by rating scales or spontaneously reported adverse events.	36/NR	3 risperidone patients withdrawn due to "sponsor decision."
Harvey 2006 (Companion to Zhong 2006) DB, RCT Inpatients for 1st week then outpatients	NR	NR/NR	Sub- analysis of Zhong K, Harvey P, Brecher M, Sweitzer D: A randomized, double- blind study of quetiapine and risperidone in the treatment of schizophrenia. Neuropsychopharmacology 2004; 29(suppl 1):S232.
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT, multicenter (US, Austria, Israel, Norway, Poland and The Netherlands)	NR	67/NR	Analysis of correlations of baseline scores on individual tests to significant change in test showed some significant findings. Dose comparisons: higher relative doses of olanzapine used than risperidone.
Harvey, 2003b (Harvey, 2002a,b,c & Harvey, 2003a all = Sub-group analysis of Conley, 2001) RCT, multicenter (US)	NR - check anticholinergic med use?	96 ((25%) 39 (10.3% of total N) due to adverse events	Analysis of correlations of baseline scores on individual tests to significant change in test showed some significant findings. Mean doses not reported.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Hatta 2008 Open-label CT pseudorandomized Multicenter (7) Japan	Inclusion: Patients in psychiatric emergency departments with acute agitation (PANSS-EC score >=15). Exclusion: Patients who refused oral medication	Patients seen during 1st month of study were assigned to olanzapine 10 mg oral disintegrating tablet. Patients seen in June were assigned to risperidone oral solution 3 mg. Same dose could be given at anytime if patient remained agitated. Patients with previously effective treatment on olanzapine or risperidone were treated with the same drug. Follow-up: 60 minutes after initial dose; 12 hours for EPS.	None	Anticholinergic meds not permitted unless acute EPS appeared. Adjunctive drugs not allowed during 1st hour of treatment.
Hatta 2009 RCT- rater blinded Psychiatric emergency centers (15) Japan	Inclusion: 18–64 years old, newly admitted as emergency cases, and met criteria of the ICD-10 for schizophrenia, acute schizophrenia-like psychotic disorder, or schizoaffective disorder. Exclusion: obvious complications such as liver dysfunction, renal dysfunction, heart failure, respiratory failure, or diabetes mellitus; were pregnant or who wanted to become pregnant	Risperidone (3–12 mg/day; n=20), Olanzapine (10–20 mg/day; n=17), Quetiapine (300–750 mg/day; n=20), or Aripiprazole (12–30mg/day; n=21),for 8 weeks	None	Benzodiazepines and anticholigenerics
Huang, 2005 RCT, blinding - NR, Taiwan Inpatients	Inclusion: Inpatients with schizophrenia according to DSM-IV. Exclusion: Systemic diseases.	conventional antipsychotic drugs (haloperidol 10–15 mg/day, sulpiride 800–1200 mg/day, and loxapine 100–150 mg/day) and atypical antipsychotic drugs (risperidone 3–5 mg/day, olanzapine 10–20 mg/day, and clozapine 100–300 mg/day) 3 weeks	1 week drug free washout	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Hatta 2008 Open-label CT pseudorandomized Multicenter (7) Japan	PANSS-EC at time 0, 15, 30, 45, and 60 min. CGI-S at time 0 CGI-C at 60 min	Mean age 38 512% male (Note: 41% in olanzapine vs. 62% in risperidone; P=0.08) Study in Japan, ethnicity NR;	Olanzapine (N=34) vs. risperidone (N=53): N (% of group) kept on drug used previously: 3 (8.8) vs. 10 (18.9) Schizophrenia, schizotypal, and delusional disorders (%): 79.4 vs. 62.3 Mood disorders (%): 11.8 vs. 15.1	853/90/87
Hatta 2009 RCT- rater blinded Psychiatric emergency centers (15) Japan	PANSS, CGI, and Global Assessment of Functioning (GAF)	Mean age 41 yrs 42% male 100% Asian	Antipsychotic-naïve 38% Schizophrenia 96% Acute schizophrenia-like psychotic disorder 1% Schizoaffective disorder 3%	813/334/80
Huang, 2005 RCT, blinding - NR, Taiwan Inpatients	Serum lipid profiles, including TC, TG, HDL, VLDL, LDL levels, and ratios of TC/HDL and LDL/HDL were measured in the hospital laboratory using enzymatic determination Blood samples were taken between 7:30 a.m. and 8:30 a.m. after the patients had fasted for at least 10 h.	Mean age 32.4 yrs 51% male Ethnicity NR	mean BMI= 23.8 mean TC=175.0 mg/dl; mean TG=110.5 mg/dl; mean HDL=43.3 mg/dl; mean VLDL=21.2 mg/dl mean LDL=110.4 mg/dl; mean TC/HDL=4.3 mean LDL/HDL=2.8	NR/126/97

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Hatta 2008 Open-label CT pseudorandomized Multicenter (7) Japan	0/0/87	Olanzapine oral disintegrating tablet (N=34) vs. risperidone oral solution (N=53) CGI-C mean (SD): 2.8 (1.3) vs. 3.2 (1.4); P=0.22 Additional injection due to worsening of symptoms, N (%): 4 (11.8) vs. 5 (9.4); P=0.73 Repeated-measures ANOVA: PANSS-EC scores decreased progressively in both groups, with no significant difference between groups (F=2.94; P=0.09).
Hatta 2009 RCT- rater blinded Psychiatric emergency centers (15) Japan	29/0/78	Risperidone vs. olanzapine vs. quetiapine vs. aripiprazole CGI-C 3.4 (1.7) vs. 2.8 (1.1) vs. 4.1 (2.1) vs. 4.4 (2.1) PANSS (mean change from baseline) Total −24.7 (27.9) vs. −33.4 (20.8) vs. −28.9 (28.6) vs.−18.4 (26.0) Positive scale −10.8 (10.9) vs. −12.6 (9.3) vs. −9.4 (8.6) vs.−6.5 (9.1) Negative scale −3.3 (5.6) vs.−5.6 (5.7) vs. −6.3 (9.5) vs. −3.8 (5.2)
Huang, 2005 RCT, blinding - NR, Taiwan Inpatients	NR/NR/97	Haloperidol - no significant changes in any of the lipid profile levels. sulpiride had significantly decreased ratio of LDL/HDL (t = 2.576, P=0.024). Loxapine decreased ratios of TC/HDL (t = 3.127, P=0.009) and LDL/HDL (t = 5.027, P=0.000). risperidone - significantly increased TC (t =2.292, P=0.032) and HDL levels (t =4.735, P=0.000) and significantly decreased ratios of TC/HDL (t = 3.065, P=0.006) and LDL/HDL (t = 3.043, P=0.006). Olanzapine - significantly increased TG level (t =2.480, P=0.026). clozapine had significantly increased TG (t =2.179, P=0.049) and VLDL levels (t =2.213, P=0.044) Changes from baseline Haloperidol vs. sulpiride vs. loxapine vs. risperidone vs. olanzapine vs. clozapine TC (mg/dl) 4.3 vs. -5.3 vs. -3.7 vs. 12.7 vs. 12.9 vs. -3.8 TG (mg/dl) 25.9 vs. 9.5 vs -26.8 vs. 8.9 vs. 50.3 vs. 28.7 HDL (mg/dl) 3.7 vs. 3.2 vs. 3.6 vs. 8.1 vs. 2.2 vs. -2.3 VLDL (mg/dl) 5.2 vs. 1.8 vs.1.0 vs. 1.7 vs. 10.1 vs. 5.9 LDL (mg/dl) 5.1 vs. -17.6 vs. -8.3 vs. 2.9 vs. 0.5 vs. -7.4 TC/HDL 0.2 vs.-0.3 vs. -0.6 vs. -0.6 vs. -0.1 vs. 0.2 LDL/HDL 0.1 vs. -0.3 vs. -0.5 vs. -0.5 vs. -0.3 vs. 0.0

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Hatta 2008 Open-label CT pseudorandomized Multicenter (7) Japan	Blood pressure and heart rate were measured at time 0, 30 and 60 min after treatment; most severe DIEPSS scores at any time during 12 hr.	Olanzapine vs. risperidone, N (%): 0 (0) vs. 3 (5.7); P=0.91 Change in heart rate (beats/min), mean: -9.2 vs. 1.1; P=0.03 1 patient with bradycardia (47 beats/min) at 60 min, a decline from 76 beats/min at time 0.
Hatta 2009 RCT- rater blinded Psychiatric emergency centers (15) Japan	Vital signs, weight, laboratory data, electrocardiography (ECG), and the Drug-induced Extrapyramidal Symptom Scale (DIEPSS)	Poorly reported AEs ; Comparisons between groups - mean change from baseline for weight (p=0.098), fasting glucose (p=0.17), cholesterol (p=0.88), or triglycerides (p=0.62). Sexual side effects and sedation were not observed.
Huang, 2005 RCT, blinding - NR, Taiwan Inpatients	NA	NA

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Hatta 2008 Open-label CT pseudorandomized Multicenter (7) Japan	Olanzapine vs. risperidone, N (%): 0 (0) vs. 3 (5.7); P=0.91	0 withdrawals 0 due to AEs	
Hatta 2009 RCT- rater blinded Psychiatric emergency centers (15) Japan	Risperidone vs. olanzapine vs. quetiapine vs. aripiprazole Extrapyramidal symptoms (DIEPSS) Any symptoms 13/20 (65%) vs. 8/17 (47%) vs. 5/20 (25%) vs. 8/21 (38%) Parkinsonism 12/20 (60%) vs. 5/17 (29%) vs. 5/20 (25%) vs. 7/21 (33%) Akathisia 5/20 (25%) vs. 2/17 (12%) vs. 2/20 (10%) vs. 4/21 (19%) Dystonia 3/20 (15%) vs. 1/17 (6%) vs. 0/20 (0%) vs. 0/21 (0%) Dyskinesia 1/20 (5%) vs. 0/17 (0%) vs. 1/20 (5%) vs. 0/21 (0%)	29 withdrawals 1 due to AEs	
Huang, 2005 RCT, blinding - NR, Taiwan Inpatients	NR	NR / NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Ingole, 2009 Open-label RCT Single site, India	Inclusion: Newly diagnosed DSM-IV patients with schizophrenia; male or females aged 18-60. Exclusion: Patients with history of taking antipsychotics before study; patients with history of diabetes mellitus; patients taking antidiabetic treatment; patients with documented cardiovascular diseases.	Oral olanzapine 5 mg two times a day Oral risperidone 3 mg two times a day 12 weeks duration	None	Rescue medications available for managing emergency and side effects: lorazepam, trihexyphenidyl, clonazepam
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT, open-label, masked ratings, multicenter (67 sites, 11 countries; US, Europe, South Africa, South America)	Patients with schizophrenia, or schizoaffective disorder considered to be at high risk for committing suicide by meeting at least one of the following criteria: 1) a history of previous attempts or hospitalizations to prevent a suicide attempt in the 3 years before enrollment, 2) moderate to severe current suicidal ideations with depressive symptoms, or 3) command hallucinations for self-harm within 1 week of enrollment.	Clozapine or olanzapine Dose determined by treating clinician Duration: 2 years	none	Any required to treat patient and reduce risk of suicide Both groups seen weekly/biweekly - clozapine group for blood monitoring, olanzapine for vital sign monitoring

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Ingole, 2009 Open-label RCT Single site, India	Primary outcomes: BMI and fasting blood sugar measured at baseline, 6 weeks, and 12 weeks. Psychiatric evaluation every 15 days.	Mean age 26 41.7% male 100% nationals of India	NR	Screened NR Eligible NR 60 enrolled
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT, open-label, masked ratings, multicenter (67 sites, 11 countries; US, Europe, South Africa, South America)	Type 1: a significant suicide attempt (successful or not), hospitalization to prevent suicide. These outcomes were assessed by a masked, 3-person Suicide Monitoring Board (SMB) Type 2: Ratings from masked psychiatrist (on-site) on the CGI-Suicide Severity or "much worse" or "very much worse" from baseline. Occurrence of a Type 1 event was also considered having met criteria for a Type 2 event.(assessed at 4-8 wk intervals) Other: time to suicide attempt (SMB validated), time to hospitalization to prevent suicide (SMB validated), number of: suicide attempts, hospitalizations to prevent suicide, and interventions to prevent suicide (non-SMB validated) Blinded psychiatrists assessed: PANSS, ISST, CDS and Covi-Anxiety scales Unblinded psychiatrists assessed: SOF, ESRS	Mean age 37.1 yrs % male: 61.4% Ethnicity: 71% White 15% Black 1.3% Oriental 13% Other	62% Schizophrenic 38% Schizoaffective Mean # suicide attempts: 3.4 83% had attempted suicide at least once 63% had attempted suicide in last 36 months 84% had been hospitalized to prevent suicide attempt 27% Treatment resistant NS difference at baseline on PANSS, CGI-SS, ISST, CDS, and Covi-Anxiety scales	1065 screened 980 eligible and enrolled (490 per group)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Ingole, 2009 Open-label RCT Single site, India	0 withdrawn 0 lost to followup 60 analyzed	Olanzapine and risperidone were both associated with significantly (p<0.001) elevated body weight and BMI at 6 and 12 weeks. Significant increase (p<0.001) in fasting blood sugar level occurred in olanzapine, but not in risperidone. Mean change ±SEM from baseline at 6weeks, olanzapine vs risperidone: Body weight (kg): 1.77 ±0.157 vs 1.17 ±0.240; p<0.05 BMI (kg/m2): 0.68 ±0.059 vs 0.48 ±0.097; p<0.05 Blood sugar level (mg/dL): 7.33 ±0.569 vs 0.30 ±0.699; p<0.001 Mean change ±SEM from baseline at 6weeks, olanzapine vs risperidone: Body weight (kg): 4.67 ±0.193 vs 2.20 ±0.246; p<0.001 BMI (kg/m2): 1.80 ±0.090 vs 0.9 ±0.101; p<0.001 Blood sugar level (mg/dL): 17.43 ±1.316 vs 1.03 ±0.652; p<0.001
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT, open-label, masked ratings, multicenter (67 sites, 11 countries; US, Europe, South Africa, South America)	24 (2.4%) never received drug 380 (39%) withdrew early: 10% withdrew consent 8% due to AE's 7% lost to follow-up 980 analyzed ITT analysis includes any data obtainable on patients who left the study, method of analyzing data for those whose data were not obtainable was not reported	Type 1 events (C vs O) HR 0.76 (95% CI 0.58 to 0.97) Cox-proportional hazard model (including treatment, # prior suicide attempts, active substance or alcohol abuse, country, sex and age group as variables): HR 0.74 (95% CI 0.57 to 0.96) Clozapine also superior on individual measures (significant suicide attempts, hospitalizations to prevent suicide) Kaplan-Meier estimates indicate SS reduction in 2-year event rate in clozapine group (p=0.02, NNT = 12) Type 2 events: (C vs O) HR 0.78 (95% CI 0.61 to 0.99) Other outcomes: Drop-outs due to unsatisfactory anti-suicidal effect: 1% vs 0% (p - 0.03) (as determined by treating physician) olanzapine: SS higher rates of antidepressants and anxiolytics used olanzapine: SS higher rates of rescue interventions to prevent suicide Suicide deaths: NS (5 clozapine, 3 olanzapine) Predictive Factors: Risk of suicide: clozapine SS < olanzapine in: Schizophrenic patients, No hospitalizations to prevent suicide w/in 36 months, 2-3 lifetime suicide attempts, no Hx alcohol abuse, smokers, high ISST, Covi-Anxiety Scale and CDI scale scores

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Ingole, 2009 Open-label RCT Single site, India	Primary outcomes: BMI and fasting blood sugar measured at baseline, 6 weeks, and 12 weeks.	Abstracted in Results
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT, open-label, masked ratings, multicenter (67 sites, 11 countries; US, Europe, South Africa, South America)	NR	Overall number NR, but stated NS difference Rate of serious AE NR, but stated NS difference Most frequent AEs: clozapine: hypersalivation, somnolence, weight gain, and dizziness olanzapine: weight gain, somnolence, dry mouth, and dizziness clozapine vs olanzapine: Somnolence 45.9% vs 24.7% (p<0.001) Weight Gain: 31.3% vs 55.6% (p<0.001) Dizziness: 26.9% vs 12.4% (p<0.001) Other AEs with SS difference: clozapine causes SS lower rate: insomnia, akathisia, muscle rigidity, dry mouth olanzapine causes SS lower rate: convulsions, postural hypotension, syncope, dysarthria, constipation, hypersalivation, dyspepsia, nausea, vomiting, urinary incontinence, weakness, WBC count decreased (5.8% vs 0.8%) Other outcomes clozapine SS lower rate than olanzapine: Suicidal ideation, suicide attempts, laceration, depression, mood alteration, mood disorder, drug abuse, alcoholism. All of these were also considered under efficacy analysis. The comparisons here are based only on patients who received drug.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Ingole, 2009 Open-label RCT Single site, India	NR	0 withdrawals 0 due to AEs	
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT, open-label, masked ratings, multicenter (67 sites, 11 countries; US, Europe, South Africa, South America)	NR	379 total Due to AE: 8.4% clozapine, 6.7% olanzapine When add in w/d due to abnormal labs or lab test procedure result: 9% clozapine, 6.7% olanzapine (NS)	Study powered to assess all significant suicide attempts (successful/non-successful). Drug and alcohol abuse found to be a significant predictor of suicide attempt, and SS > drug abuse in the olanzapine group reported as AE. Baseline prevalence of use not reported. Mean doses seem non-comparable; mean dose clozapine = 274mg (+/- 155 SD), mean dose olanzapine = 16.6mg (+/- 6.4mg SD).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Jerrel, 2002 RCT, open-label with economic analysis	Medicaid patients age 18-54, with schizophrenia or schizoaffective disorder and >/= 2 acute psychiatric hospitalizations within 12 months, and noncompliant with outpatient treatment and not taking atypical antipsychotics for 6-8 weeks or more during the prior 3 months. Patients screened during acute inpatient stay.	olanzapine, risperidone or continue on typical antipsychotic as prescribed. Doses determined by treating physician. Average doses: olanzapine: 12-15mg/d risperidone: 4-6mg/d haloperidol: 14-17mg/d Duration: 12 months	Acute treatment prior to randomization using short-acting typical antipsychotics. Discontinuation and titration determined by treating physician	Discretion of treating physician
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT, multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conf proc	Patients aged 60+ with chronic schizophrenia or schizoaffective disorder; without dementia; with baseline PANSS score range 50-120, inpatient (hospitalized </= 4wks at screening) or outpatient (including nursing home, boarding care and hospitalized patients receiving only board and care).	olanzapine: flexible dose 5-20mg/d mean modal dose: 11.1 mg risperidone 1-3mg/d mean modal dose: 1..9 mg Duration: 8-weeks	1 week washout period	lorazepam

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Jerrel, 2002 RCT, open-label with economic analysis	PANSS, BPRS, DIS-III-R depression and Mania Modules, RFS, SAS-SM, DISCUS, CUAD, CSQ-8, S-A EPS, BAS every 3 months Prescribing of study and other allowed drugs, refills, and other compliance indicators were abstracted from medical records. Service utilization: number and duration of hospitalizations, outpatient service use per 3-month follow-up period	Mean age 36.91 68% male 29% white	72% schizophrenic Mean prior inpatient admits: 9.75 Acute hospitalization days in past 6 mos: 12.56 Atypical antipsychotic use: 29% Supplemental antipsychotic use: 17% Anti-EPS med use: 72% Taking mood stabilizer: 49%	NR/343/343 Final group of 108: olanzapine 30 risperidone 36 Typicals 42
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT, multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conf proc	Change from baseline PANSS total score Clinical Improvement defined as 20% decrease in total PANSS Secondary measures: HAM-D, CGI-s and CGI change Cognitive assessments (see Harvey 2003) Assessed at weeks 0, 1, 2, 3, 4, 6, 8	Mean age: 71.1 35% male 77% white 17% black 3% Hispanic 2% Asian	85% schizophrenia 15% schizoaffective disorder mean baseline PANSS score: 77.1	203/176/175

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Jerrel, 2002 RCT, open-label with economic analysis	235/ NR /108 Patients or physician could withdraw patient after randomization but prior to receiving medication. 74 patients refused 146 physicians refused to have patients enrolled	Treatments Received: Logistic regression analysis: Prescribed assigned med significantly decreased over time (OR 0.19 (95% CI 0.09 to 0.43), but NS between groups Compliance with assigned med, odds of being prescribed a supplemental antipsychotic, odds of being prescribed a mood stabilizer were higher with risperidone vs typicals, and olanzapine vs typicals, but no difference between atypicals. PANSS positive: NS group x time interaction, but scores SS decreased over time PANSS negative: NS group x time interaction, but scores SS decreased over time BPRS: NS group x time interaction, but scores SS decreased over time DIS-II-R Mania and Depression scores: NS group x time interaction, but scores SS increased over time CUAD: NS group x time interaction, but scores SS decreased over time RFS: NS group x time interaction, but role functioning SS decreased over time Self-report Psych Function: NS group interaction effect Time to Discharge: Kaplan-Meier Survival Analysis and Cox proportional hazard analysis: NS difference between groups Time to Rehospitalization: Kaplan-Meier Survival Analysis and Cox proportional hazard analysis: NS difference between groups: Client satisfaction: NS by group, but increased over 1st 3 months (p<0.03)
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT, multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conf proc	41/1/174	Baseline PANSS score reduced by >=20%: 58% risperidone, 59% olanzapine (within groups P<0.005). Change in mean Ham-D score: -1.8 risperidone (p<0.01, within group) -1.5 olanzapine (p<0.05, within group). CGI improved in 32.5% risperidone, 36% olanzapine. Between-group differences NS for PANSS, Ham-D, and CGI.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Jerrel, 2002 RCT, open-label with economic analysis	Use of Anti-EPS drugs, DISCUS, S-A EPS, GBAS	Use of Anti-EPS drugs: SS decrease in use over time (OR 0.51 (95% CI 0.28 to 0.90), but no difference between groups After controlling for time-dependent effects of anticholinergic drug use: DISCUS: SS time effect; decrease from baseline to 12 months (p =0.0007) S-A EPS SS time effect; lower scores from baseline to 12 months (p<0.0001) GBAS: SS decrease in ratings baseline to 12 months (p=0.002)
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT, multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conf proc	Elicited by investigator ESRS EPS medications Weight	Risperidone vs olanzapine: Somnolence 13.8% vs 13.6% (ns) Insomnia 16.1% vs 10.2% (ns) Dizziness 10.3% vs 11.4% (ns) EPS 9.8% vs 15.9% (ns) 7% Weight gain 5.1% vs 14.8% (p=0.043)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Jerrel, 2002 RCT, open-label with economic analysis	Use of Anti-EPS drugs: SS decrease in use over time (OR 0.51 (95% CI 0.28 to 0.90), but no difference between groups After controlling for time-dependent effects of anticholinergic drug use: DISCUS: SS time effect; decrease from baseline to 12 months (p =0.0007) S-A EPS SS time effect; lower scores from baseline to 12 months (p<0.0001) GBAS: SS decrease in ratings baseline to 12 months (p=0.002)	NR (3 patients not included in rehospitalization analysis due to never being discharged from index hospitalization)	Study focused on patients with recent hospitalizations and who were either non-compliant with treatment or whose treatment was not stabilized.
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT, multinational (US, Israel, Poland, Norway, The Netherlands, Austria) 1 full paper, 2 conf proc	EPS 9.8% vs 15.9% (ns) 7% Weight gain 5.1% vs 14.8% (p=0.04)	Total: 41/175 (23%) Due to AE: 5.7% risperidone, 5.7% olanzapine	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Kane 2009 DB RCT Multinational, multicenter (60)	Inclusion: Inpatients or outpatients; 18-65 yrs; schizophrenia diagnosis; initial PANSS 75 or more; minimum of 4 on one of PANNS positive; CGI-S of 4 or more at screening and randomization; CGI-I 3 or more at randomization Exclusion: Pregnancy; lactation; significant medical illness	Olanzapine vs. aripiprazole Mean doses 16.7 vs. 19.3 mg/day 28 weeks	2-9 day screening	Benzodiazepines
Kane, 2007 DB, RCT, placebo and active-controlled, multicenter (Europe and India)	Inclusion: Male or female; ≥18 years; acute episode of schizophrenia; diagnosed with schizophrenia according to DSM-IV criteria for at least 1 year prior to screening and have agreed to voluntary hospitalization for a minimum of 14 days. Exclusion: Substance dependence within 6 months, a medical condition that could affect absorption, metabolism or excretion of the study drug; tardive dyskinesia or neuroleptic malignant syndrome; significant risk for suicide or violent behavior,; pregnant or breastfeeding, patients receiving a depot antipsychotic within 120 days or paliperidone palmitate.	Paliperidone ER 6 mg, 9 mg, 12 mg Placebo Olanzapine 10mg 6 weeks	3 day washout	Benzodiazepine and antidepressants assuming a stable dose for at least 3 months and benztropine 1 or 2 mg twice daily or biperiden 2 mg three times daily was also permitted for the treatment of movement disorders

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Kane 2009 DB RCT Multinational, multicenter (60)	Time to all-cause treatment discontinuation, change in PANSS, CGI-s and -I	Mean 38 years 68% male 30% White 31% African descent 32% Hispanic 7% other	16% inpatients and 84% outpatients	726/645/566
Kane, 2007 DB, RCT, placebo and active-controlled, multicenter (Europe and India)	PANSS and Clinical and Global Impressions–Severity (CGI-S) scale scores baseline, Days 4, 8 and 15, and then every 7 days up to and including Day 43. Personal and social functioning as determined using the PSP scale was assessed at baseline and end point.	Mean age 37.1 years 52% male 86% white <1% Asian 14% other	Age at diagnosis 27.0 years Baseline PANSS total 93.9	680/NR/630

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Kane 2009 DB RCT Multinational, multicenter (60)	263/47/566	Olanzapine vs. aripiprazole CGI-I 2.7 vs. 2.8 P = 0.279 Change in PANSS -30.2 vs. -25.9 P = 0.014 PANSS-P -5.9 vs. -5.0 P = 0.025 PANSS-N -8.8 vs. -7.6 P = 0.053 CGI-S -1.2 vs. -1.1 P = 0.336
Kane, 2007 DB, RCT, placebo and active-controlled, multicenter (Europe and India)	215/7/628	Placebo - palperidone6 - paliperidone9 - paliperidone12 Total PANSS score mean (SD) Baseline 94.1 (10.7) 94.3 (10.5) 93.2 (11.9) 94.6 (11.0) Change from baseline −4.1 (23.2) −17.9 (22.2) −17.2 (20.2) −23.3 (20.1) p-value < compared to placebo 0.001 0.001 0.001 ≥30% decrease in PANSS total paliperidone6 =56%, paliperidone9 =51%, paliperidone12 =61%, placebo=30%; p< 0.001 for all paliperidone ER groups versus placebo. classified as ‘marked’ or ‘severely ill’ on the CGI-S scale baseline vs. endpoint paliperidone6 62.6% versus 21.3% paliperidone9 57.3% versus 23.0% paliperidone12 64.4% versus 16.3% placebo 59.5% versus 50.8% olanzapine 64.1% versus 23.5%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Kane 2009 DB RCT Multinational, multicenter (60)	Patient reported, lab tests, vital signs, SAS, BAS and AIMS	Olanzapine vs. aripiprazole Insomnia 16.7 vs. 27.4 P = 0.002 Weight increase 16.4 vs. 7.0 P = 0.001 Somnolence 14.6 vs. 8.4 P = 0.025 Headache 11.7 vs. 17.5 Increased appetite 11.7 vs. 6.7 P = 0.047 Anxiety 7.8 vs. 10.9 Fatigue 7.8 vs. 6.3 Dizziness 6.8 vs. 8.4 Dry mouth 6.8 vs. 5.3 Exacerbation of schizophrenia 6.4 vs. 5.6 Sedation 6.4 vs. 2.8 P = 0.046 Nausea 6.0 vs. 8.1 Akathisia 5.3 vs. 9.1 Depression 3.9 vs. 1.1 P = 0.032 Upper abdominal pain 1.8 vs. 5.3 P = 0.038
Kane, 2007 DB, RCT, placebo and active-controlled, multicenter (Europe and India)	Voluntary report of AE at every scheduled visit. Treatment emergent glucose-,prolactin-,and EPS-related AE's as defined by WHO AE terms. AIMS, BARS, SAS days 8-15 and every 7 days up to and including day 43. Clinical lab evaluations, ECG, vital signs, physical examination and assessment of bodyweight.	

	Placebo	Paliperi-done6	Paliperi-done9	Paliperi-done12	Total paliperi-done	Olanzapine
Total # s/AEs	79 (63)	74 (60)	77 (63)	95 (73)	346 (66)	81(63)
Psychiatric disorders						
Insomnia	22(17)	14 (11)	20 (16)	16 (12)	50 (13)	18 (14)
Somnolence	7 (6)	5 (4)	8 (7)	10 (8)	23 (6)	18 (14)
Agitation	7 (6)	8 (7)	5 (4)	3 (2)	16 (4)	3 (2)
Anxiety	7 (6)	5 (4)	5 (4)	6 (5)	16 (4)	7 (5)
Psychosis	8 (6)	4 (3)	0	4 (3)	8 (2)	4 (3)
Central and peripheral nervous system disorders						
Extrapyramidal disorder	1 (1)	4 (3)	9 (7)	13 (10)	26 (7)	2 (2)
Hyperkinesia	4 (3)	4 (3)	7 (6)	14 (11)	25 (7)	5 (4)
Headache	10 (8)	1 (1)	8 (7)	10 (8)	19 (5)	8 (6)
Hypertonia	0	1 (1)	7 (6)	5 (4)	13 (3)	0
Heart rate and rhythm disorders						
Tachycardia	13 (10)	22 (18)	17 (14)	29 (22)	68 (18)	18 (14)
Gastro-intestinal system disorders						
Saliva increased	1 (1)	1 (1)	2 (2)	10 (8)	13 (3)	0
Vomiting	2 (2)	2 (2)	2 (2)	6 (5)	10 (3)	1 (1)
Cardiovascular disorders, general						
ECG abnormal specific	3 (2)	4 (3)	5 (4)	9 (7)	18 (5)	2 (2)
Hypotension postural	1 (1)	4 (3)	3 (2)	7 (5)	14 (4)	6 (5)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Kane 2009 DB RCT Multinational, multicenter (60)	Olanzapine vs. aripiprazole Change in BAS -0.1 vs. -0.1 Change in SAS -1.2 vs. -0.9 Change in AIMS -0.5 vs. -0.2	263 withdrawals 53 due to AEs	
Kane, 2007 DB, RCT, placebo and active-controlled, multicenter (Europe and India)	Akathisia, as assessed by the BARS, was rated as absent 92%–93% paliperidone6 and placebo 90% of the paliperidone9 87% of the paliperidone12. 93% olanzapine use of anti-cholinergic medication 6% placebo 11% paliperidone6 17% of the paliperidone9 22% of the paliperidone12 8% olanzapine	215 withdrawals 38 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Karagianis 2009 DB RCT Multicenter Canada, the Netherlands, USA and Mexico The PLATYPUS Study	Inclusion: 18–65 years; a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform, bipolar disorder or other related psychotic disorder and had gained > 5 kg or an increase in BMI > 1 kg/m3 Exclusion: ODO treatment in the preceding six months, had a medical condition or were taking other medications that could influence weight, or were participating in a weight-loss program.	Standard olanzapine tablets (SOT) vs. orally disintegrating olanzapine (ODO) tablets; patients continued treatment with 5–20 mg olanzapine in a flexible, single daily dose and were randomly assigned (1:1) to receive ODO plus oral placebo, or sublingual placebo plus SOT for 16 weeks.	None	NR
Keefe, 2006 DB, R, X 1 year Multicenter: North America (US and Canada) conducted July 1999-Nov. 2000.	18-55 years of age; schizophrenia or schizoaffective disorder, and a minimum score of 4 on at least 2 positive items on PANSS; score of 18 or more on BPRS; English speaker, level of understanding sufficient to agree to all tests and examinations, illness duration of at least 2 years from first hospitalization and/or diagnosis/treatment.	olanzapine: 5-20 mg/day (mean dose 12.3mg/day) risperidone: 2-10 mg/day (mean dose 5.2mg/day) or haloperidol: 2-19 mg/day or (mean dose 8.2mg/day) Initial 8 weeks (flexible dosing); thereafter a fixed dosed based on investigator's judgment	none	antidepressants, except fluvoxamine and lithium. Acute usage of valproic acid, carbamazepine, antiemetics, and steroids. Benztropine mesylate or biperiden (up to 6mg/day)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Karagianis 2009 DB RCT Multicenter Canada, the Netherlands, USA and Mexico The PLATYPUS Study	Weight; Waist circumference; metabolic syndrome was assessed using ATP III criteria (National Institutes of Health, 2001). Homoeostasis model assessment for insulin sensitivity was based on the model of Mathews et al.	Mean age 39 yrs 54.4 % male 52.3% Caucasian 33.6% Hispanic 10.1% Black 2% Asian 1.3% First-nation 0.7% Other	Schizophrenia 55% Bipolar 27.5% Schizoaffective disorder 10.1% Schizophreniform 6% Other 1.3%	186/153/149
Keefe, 2006 DB, R, X 1 year Multicenter: North America (US and Canada) conducted July 1999-Nov. 2000.	Weekly visits x first 4 wks; then biweekly visits x 4 wks; then monthly. Neurocognitive score were assessed at baseline, 8, 24, 52 weeks. Executive Function, Trails B and WCST 64 card version, Learning and Memory, Rey AVLT and Crawford Alternative; Words recalled after delay; Rey-Osterrieth Complex Figure; Processing Speed, WAIS-R Digit Symbol, Trails A; Attention/Vigilance, Continuous Performance Test; Working Memory, WAIS-3 Letter-number Sequencing; Verbal Fluency, Controlled Oral Association Test, Category Instances; Visuospatial Ability, Rey-Osterrieth Complex figure test; Motor Function, Grooved Pegboard. Secondary efficacy Measures: PANSS, MADRS, HAMA)	Mean age: 39 Male: 295 (71.3%) 59.7% Caucasian 28.3% African 0.5% Western Asian 1.4% East/Southeast Asian 6.8% Hispanic 3.8% Other origin	40.6% -previously admitted to the hospital in past year due to psychiatric problems 40.9% O; 48.1% R; and 61.9% H used anticholinergic medication at any time during the trial; p<0.01. Mean PANSS total score was 82.1 at baseline. Mean PANSS positive score for pts randomized prior to dropping the haloperidol arm was significantly lower when compared to pts randomized after haloperidol arm was dropped, p=0.007	NR/NR/414

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Karagianis 2009 DB RCT Multicenter Canada, the Netherlands, USA and Mexico The PLATYPUS Study	27/7/149	ODO vs. SOT BMI, kg/m2 0.52±0. vs. 2 0.72±0.2 P = 0.465 Weight, kg 1.42±0.5 vs. 2.08±0.6 P = 0.385
Keefe, 2006 DB, R, X 1 year Multicenter: North America (US and Canada) conducted July 1999-Nov. 2000.	174 / 90 /339* *=number evaluated at week 52 for neurocognitive composite score based on sample's baseline data	Neurocognitive Efficacy: Primary: Sample composite LOCF: No significant difference between any of the tax groups at weeks 8, 24, 52; p=NS 52 week endpoint: z-scores based on sample composite mean ± SD: 0: 17 ± 0.51; p<0.01, R: 0.18 ± 0.46; p<0.01 Sample composite OC: R. vs. O, p=NS 52 week endpoint: Mean change within O group, p<0.01 and R p<0.01 treatment groups. Normative composite LOCF: change in composite scores was not significantly different between group; p=NS 52 week endpoint: Within group improvement: O group, p<0.01; R group, p<0.01 Normative composite OC: No significant difference between O and R 52 week endpoint: Within-group improvement: O group, p<0.01; R group, p<0.01 Individual neurocognitive domains: 52 week LOCF mean change from baseline: O vs R, p=NS. O improved on all domains (all p=0.04) except visuospatial ability and verbal fluency; R improved on all domains (all p<0.05) except verbal fluency. Normative neurocognitive domains 52 week LOCF mean change from baseline: "similar profile was found" (data not shown) Secondary: PANSS depression: 52 week LOCF mean change from baseline pairwise group: O vs R for PANSS total, positive score, and negative score: p=NS. LOCF at 52 weeks: all treatment groups significantly improved on all three PANSS measurement: p<0.02. MADRS or HAMA-No statistical differences between any tax groups 52 week visit-wise OC: within group: O, p<0.001; R, p<0.001 52 week OC pairwise group: O vs. R; NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Karagianis 2009 DB RCT Multicenter Canada, the Netherlands, USA and Mexico The PLATYPUS Study	Spontaneously reported	ODA vs. SOT Increased appetite 9 (10.7) vs. 10 (15.4) Headache 5 (6.0) vs. 5 (7.7) Somnolence 5 (6.0) vs. 5 (7.7) Anxiety 3 (3.6) vs. 2 (3.1) Constipation 3 (3.6) vs. 1 (1.5) Decreased appetite 3 (3.6) vs. 0 (0.0) Depression 3 (3.6) vs. 2 (3.1) Fatigue 3 (3.6) vs. 5 (7.7) Akathisia 2 (2.4) vs. 2 (3.1) Insomnia 2 (2.4) vs. 3 (4.6) Dizziness 1 (1.2) vs. 4 (6.2) Dry mouth 1 (1.2) vs. 2 (3.1) Dyspepsia 1 (1.2) vs. 2 (3.1) Nasopharyngitis 1 (1.2) vs. 3 (4.6) Tremor 1 (1.2) vs. 2 (3.1) Arthralgia 0 (0.0) vs. 2 (3.1) Influenza 0 (0.0) vs. 2 (3.1)
Keefe, 2006 DB, R, X 1 year Multicenter: North America (US and Canada) conducted July 1999-Nov. 2000.	TEAE, vital signs (weight), laboratory tests at every scheduled visit AISM, Barnes Akathisia, and Simpson-Angus scales assessed every week through week 4, every other week through week 8, and then every other month	Treatment-emergent AE in > 10% of any group or significantly different between groups: Olanzapine > R: somnolence, depression, headache, insomnia, anxiety, nausea, weight gain, pain, rhinitis, hallucinations, nervousness, dry mouth, diarrhea, dizziness, akathisia, tremor, paranoid reaction, abnormal thinking, vomiting, agitation, (each p= NS) Constipation: O> R; p=0.01 Mean change from baseline to 52 week endpoint: Weight (kg) gain: O > R: p<0.01 Triglyceride mean change: O> R, p=0.01 Cholesterol mean change (mg/dL): O > R; <0.01 Glucose, non-fasting (mg/dL): O vs. R; p=NS Prolactin mean change: (ng/mL): R > O; p <0.01

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Karagianis 2009 DB RCT Multicenter Canada, the Netherlands, USA and Mexico The PLATYPUS Study	NR	27 withdrawals 4 due to AEs	
Keefe, 2006 DB, R, X 1 year Multicenter: North America (US and Canada) conducted July 1999-Nov. 2000.	AIMS Total Mean Change Score: O vs. R; p=NS Barnes Global Mean Change Score: O vs. R; p=NS Simpson-Angus Total Mean Change Score: O vs. R; p=NS Akathisia: Olanzapine 8.8%, Risperidone 12.7%	269/53 O: 15 (9.4%) R:24 (15.2%) Haloperidol: 14 (14.4%)	After ~52 weeks of enrollment, the haloperidol arm was dropped due to recruitment difficulties. After the study was completed, it was discovered that 17.7% O group, 14.1% R , and 18.6% H group were on antipsychotic medications prior to randomization. Approx. 25.8% were randomized to the same antipsychotic medication they were taking prior to enrollment (18% olanzapine, 14% risperidone). 61% of pts were considered to be compliant with prescribed treatment. Relapse Rate: Pts who responded: No difference Pts who stabilized: O: 15/129, 11.6%; R 27/121, 22.3%; p=0.03.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Keks, 2007 RCT	Diagnosis of schizophrenia or schizoaffective disorder ; PANSS total score 50 or over at least 18 years; BMI not exceeding 40 mg/ kg2; within the previous 2 months the patient had been hospitalized or required medical intervention for an acute exacerbation of psychosis and had experienced an additional acute exacerbation during the previous 2 years.	long-acting risperidone (25mg or 50mg every14 days) or olanzapine (5-20mg/day). 13 weeks and one year	1 week of wash-out and introduction of new drug	Long-acting risperidone vs. olanzapine concomitant medication: 85% vs 80% sedates/hypnotics: 65% vs 53% antidepressants: 43% vs 34% antiparkinsonian drugs: 37% vs 18% anticonvulsants: 21% vs 19% muscle relaxants: 11% vs 10%
Kelly, 2005 DB, RCT Thyroid results from Conley 2003 (different from the Conley 2003 above)	Treatment-resistant schizophrenia and medically healthy.	N=38 400 mg/day quetiapine, or 4 mg/day risperidone, or 12.5 mg/day fluphenazine 6 weeks duration	NR	lorazepam, benztropine, oral hypoglycemics, laxatives, diuretics, nonsteroidal anti-inflammatory agents, antibiotics, antihypertensives

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Keks, 2007 RCT	PANSS, clinical improvement was defined as a 20% or greater reduction in PANSS total scores, CGI-S, Wisconsin Quality of Life Index at baseline (randomization), weeks 5, 9, 13, 25, 37 and 53 and at end-point	Long-acting injection vs olanzapine: Mean age: 35 years Male: 56% vs 58% Caucasian: 96% vs 97%	Age at diagnosis 26.5	693/NR/629
Kelly, 2005 DB, RCT Thyroid results from Conley 2003 (different from the Conley 2003 above)	Blood drawn at baseline, and at end of study. Tests included: total serum thyroxine, free thyroxine index, serum T3 resin uptake, TSH	Mean age: 43.8 Male: 73% Black: 60% White: 40%	NR	NR/NR/38

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Keks, 2007 RCT	200/NR/ short-term 378 and long-term 362	Risperidone vs. olanzapine Short-term mean (s.d..) and LSM of the difference (95% CI) PANSS Total change at endpoint -16.9 (15.5) vs. -17.8 (15.4) and 0.2 (-2.7 to 3.0) Long-term mean (s.d..) and LSM of the difference (95% CI) PANSS Total change at endpoint -20.4 (18.8) vs -20.5 (20.3), 0.2(-3.4 to 3.8) Anxiety/depression change at endpoint -3.1 (3.6) vs. -3.4 (3.7) and 0.6 (0.1 to 1.2) P < 0.05 CGI- S at endpoint (not or mildly ill) 66% vs. 67%
Kelly, 2005 DB, RCT Thyroid results from Conley 2003 (different from the Conley 2003 above)	NR/NR/30	Change in Thyroid Function Test Results: Mean + SD Change Total serum thyroxine: Q: -2.37 + 1.48 vs R: -0.01 + 1.02 vs F: 0.62 + 1.91; p=.01 Free thyroxine index: Q: -0.76 + 0.68 vs R: -.0.07 + 0.48 vs F: 0.22 + 0.62; p=NS Serum T3 resin uptake: Q: -0.00 + 2.76 vs R: 0.38 + 1.92 vs F: 0.30 + 1.36; p=NS Thyroid-stimulating hormone: Q: -0.86 + 1.6 vs R: -0.28 + 1.05 vs F: -0.49 + 1.68; p=NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Keks, 2007 RCT	Adverse events were recorded at each visit. Severity of movement disorders was assessed by means of the Simpson–Angus Rating Scale at baseline, at weeks 13, 25, 37 and 53 and end-point.	Risperidone vs. olanzapine (%) Psychosis 29 vs. 25 Insomnia 22 vs. 14 Depression 20 vs. 14 Anxiety 14 vs. 16 Agitation 10 vs. 5 Headache 8 vs. 5 Hyperkinesia 8 vs. 3 Rhinitis 7 vs. 6 Weight increase 6 vs. 9 Somnolence 5 vs. 7 Tremor 5 vs. 2 Injury 5 vs. 2 Serious 23 vs. 21
Kelly, 2005 DB, RCT Thyroid results from Conley 2003 (different from the Conley 2003 above)	NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Keks, 2007 RCT	Extrapyramidal symptoms risperidone 25% vs olanzapine 15% (p<0.05)	200 total withdrawals 18 due to AEs	
Kelly, 2005 DB, RCT Thyroid results from Conley 2003 (different from the Conley 2003 above)	NR	NR / NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	Treatment resistant schizophrenia: 1. Persistent positive psychotic symptoms: item score ≥ (moderate) on at least 2 of 4 positive symptom items on BPRS; 2. Presence of at least moderately severe illness on total BPRS score (score ≥ 45 on the 18-item scale) and a score of ≥4 (moderate) on CGI; 3. Two failed historical trials of antipsychotics of at least 6 weeks duration at doses of at least = to 600mg/day chlorpromazine; 4. No stable period of good social and/or occupational functioning within the last 5 years.	Risperidone: 4mg/day (n=12) Quetiapine: 400mg/day (n=6) OR fluphenazine 12.5mg/day (n=9) x 12 weeks	4-6 week lead in traditional antipsychotic medication (7 were on olanzapine)	agitation or anxiety: up to 10mg/day of lorazepam prn; Benztropine mesylate (up to 4 mg/day); propranolol (30-120 mg/day) for EPS
Kelly, 2008 goes with Conley 2001 DB RCT	Schizophrenia or Schizoaffective disorder by DSM-IV diagnosis, baseline PANSS score, 60–120, aged 18–64 years; out- or inpatients hospitalized ≤4 weeks.	Risperidone 2–6 mg/d (flexible dose); oral Olanzapine 5–20 mg/d Duration: 8 weeks Both drugs given once daily according to following regimens: days 1–2, 2 mg Risperidone or 10 mg Olanzapine; days 3–7, 2–4 mg risperidone or 5–10 mg Olanzapine; days 8–14, 2–6 mg risperidone or 5–15 mg Olanzapine; days 15–56, 2–6mg Risperidone or 5–20 mg Olanzapine	1 week gradual dis-continuation	NR
Kern, 2006 RCT, open-label	Inclusion - outpatients, schizophrenia or schizoaffective disorder, between ages of 18 and 65, able to speak and understand English, were on a stable dose of an oral typical antipsychotic, risperidone, or quetiapine for at least 1 month, and had not been hospitalized for psychiatric treatment for at least 2 months. Exclusion - current suicidality, neurological disorder (e.g., epilepsy), acute or unstable medical condition, a clinically significant laboratory test value, gastrointestinal resection or stapling that may interfere with study medication absorption, and alcohol- or substance-dependence within the past 3 months; received aripiprazole in a prior clinical study, had taken a selective serotonin reuptake inhibitor within 2 weeks before screening, or if they had taken an investigational drug within 4 weeks	30 mg of oral aripiprazole or 15 mg of oral olanzapine	NA	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	Changes in Sexual Functioning Scale (CSFQ) semi-structured interview at BL and endpoint BPRS ratings: weekly throughout the study	Age: R: 46; Q 42; F 45 Gender: (male) R 75%; Q: 67%; F: 88% Race: (Black) R: 50%; Q 67%; F 56%		NR/NR/38
Kelly, 2008 goes with Conley 2001 DB RCT	Total cholesterol, HDL-C, LDL-C, triglycerides, HBa1C, weight at baseline, weeks 2,4,6,8	Mean age: risperidone 41.0 (11.0) years olanzapine 38.9 (10.5) years 72.7% male Ethnicity NR	79% were outpatients Schizophrenia (n= 325) or schizoaffective disorder (n= 52) Duration of illness: mean risperidone 16.5 (10.5) years, olanzapine 15.4 (10.6) years Weight olanzapine 82.7 kg risperidone 83.7 kg BMI olanzapine 28.15 kg/m, risperidone 28.78	NR/NR/377 Risperidone 188 Olanzapine 189
Kern, 2006 RCT, open-label	California Verbal Learning Test, Benton Visual Retention Test–Revised, Wisconsin Card Sorting test, Trail Making A and B, Verbal fluency (letter and category), Letter–Number Sequencing subtest from the WAIS-III, Grooved Pegboard test, Continuous Performance Test–Identical Pairs version, and PANSS; at baseline, weeks 8 and 26.	Mean age: 40 64% male 60% Caucasian		NR/NR/255

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	18*/ NR/ 28 *4-risperidone (31%); 5 on quetiapine (42%) and 9 on fluphenazine (69%)	Sexual Dysfunction: 7/9 F (78%); 5/12 R (42%); 3/6 q (50%); P=NS Sexuality at end of study: subjective improvement: 1/8 F (13%); 6/11 R (55%); 2/5 Q: 40%; p=NS Orgasm: Q: significant improvement ; not seen with R and F; p=0.033 Arousal: Q: improved, not seen with R and F; p=NS Post-hoc analysis: (data not shown) Higher prolactin levels were correlated to lower BPRS scores. Total BPRS scores; p=0.048 positive symptoms, p=0.050 Trend was noted for activating symptoms, p=0.051. Higher prolactin levels were associated with higher negative symptoms, p=0.037. (Significant findings were not evident by drug group)
Kelly, 2008 goes with Conley 2001 DB RCT	Risperidone 53/NR/188 Olanzapine 43/NR/189	Weight gain at week 8 olanzapine 3.8 kg vs. risperidone 2.0 kg P < 0.001 BMI increase at week 8 olanzapine 1.3 kg/m risperidone 0.7 kg/m P < 0.001 Total cholesterol olanzapine 13.5 vs. risperidone -3.9 mg/dl P = 00.058
Kern, 2006 RCT, open-label	146 (57%)/21 (8%)/169	General cognitive functioning - aripiprazole and olanzapine showed significant improvement from baseline at week 8 (p=0.023 and 0.015, respectively) that fell to a trend at week 26 (p=0.055 and 0.087, respectively). No significant between-group differences at either week 8 or 26 comparisons Executive functioning - LOCF analyses failed to show significant improvement from baseline to week 8 or 26 for either group (all p>0.20) Verbal learning -, aripiprazole showed a significant improvement from baseline at both week 8 (p<0.0001) and week 26 (p<0.0001); olanzapine did not. Examination of between-group differences revealed a significant difference in favor of the aripiprazole group compared to the olanzapine group at both week 8 (p=0.020) and week 26 (p=0.040)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	Prolactin Related Adverse Event Questionnaire (PRAEQ): semi-structured interview at baseline and endpoint. Plasma prolactin: drawn prior to AM meals at baseline and at 12 weeks.	12 week prolactin levels: R: 50.6± 40.4, F: 24.4± 18.5; Q: 8.2 ±4.4, p=0.005, controlling for baseline and sex R: galactorrhea and gynecomastia 1/9 males (11%), amenorrhea: 2 females (100%) F: gynecomastia:1 female: No hormonal effects were noted in males Q: No hormonal side effects occurred; 1 out of 2 women with amenorrhea regained menstruation during Q treatment All cases of gynecomastia resolved during treatment No difference btw groups for the following: Headache: 48.1%; somnolence; 37%; insomnia 29.6%; lethargy, increased appetite and orthostasis 25.9%; dry mouth, nausea, constipation 18.5%; blurry vision, dizziness, dyspepsia, diarrhea, and anxiety 18.5% Mean prolactin levels for: pts experiencing sexual dysfunction (all drugs) were 29.25 ± 27.44 mg/dl pts with no sexual dysfunction the mean levels were 35.56 ± 41.63; p=NS.
Kelly, 2008 goes with Conley 2001 DB RCT	NR	NR
Kern, 2006 RCT, open-label	NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	NR	7 total withdrawals NR due to ASs	Sexual dysfunction was defined as "any trouble maintaining an erection, painful prolonged erections, trouble ejaculating when wanted, loss of interest once aroused, and/or not able to have an orgasm if wanted. " Sexual dysfunction was not found to be correlated with prolactin levels (p>0.05). Those on quetiapine who noted "improvement" in sexual functioning tended to have a larger decrease in prolactin than for the subjects reporting no improvement (-44.25 vs. -32.57 mg/dl). No trends noted for R or F in relation to prolactin levels and subjective sexual function changes. Limitations: sample size; few subjects received O during lead-in phase
Kelly, 2008 goes with Conley 2001 DB RCT	NR	Risperidone 53/188 (28.2%) Due to AE 22/188 (11.7%) Olanzapine 43/189 (22.8%) Due to AE 17/189 (8.99%)	
Kern, 2006 RCT, open-label	NR	146 total withdrawals 46 due to AEs	Withdrawals (53%) from the olanzapine group and (62%) from the aripiprazole group.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Kinon, 2006a DB, RCT, multicenter (40 US centers)	Age 18-65 yrs; met DSM-IV criteria for schizophrenia or schizoaffective disorder; had prominent depressive symptoms defined by score >/= 16 on MADRS and score >/=4 on item 2 of MADRS. Exclusion criteria: history of nonresponse to at least 6 wks of olanzapine or ziprasidone; received a depot neuroleptic within 2 wks of visit 1.	olanzapine (n=202): 10, 15, or 20 mg/d ziprasidone (n=192): 80, 120, or 160 mg/d Doses were fixed by end of week 2 24 week study	During 2 wk titration phase, patients were titrated off previous antipsychotic medication	Concomitant medications with psychotropic activity were not allowed with the following exceptions: benzodiazepines, hypnotics, medication for treatment of EPS (excluding prophylaxis) and antidepressants if taken in stable doses for at least 30 days before enrollment and maintained throughout study
Kinon, 2006b DB, RCT, U.S. (Journal of Clinical Psychopharmacology)	Inclusion: Outpatients; DSM IV schizophrenia or schizoaffective disorder; met criteria for prominent negative symptoms, defined as a Positive and Negative Syndrome Scale (PANSS) score > 4 (moderate) on at least 3, or > 5 (moderately severe) on at least 2 of the 7 negative scale items; and for social and functional impairment, defined as a Global Assessment of Functioning Scale (GAF) score of less than or equal to 60 (moderate difficulties). Exclusion criteria: NR	Olanzapine 10-20 mg/d Quetiapine 300-700 mg/d 6 months	None	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Kinon, 2006a DB, RCT, multicenter (40 US centers)	CDSS total score at 8 weeks CDSS, MADRS, PANSS, GAF change from baseline to 24 week endpoint	Age: NR Gender: NR Ethnicity: NR	Outpatients: 99.0% olanzapine vs. ziprasidone Use of antipsychotics within 30 days before baseline: 70.8% vs. 82.3% MADRS mean (SD): 27.3 (6.2) vs. 27.3 (6.5) PANSS: 79.6 (17.5) vs. 79.1 (17.3) Concurrent use of antidepressants upon study entry: 51.1% vs. 54.7%	NR/NR/394
Kinon, 2006b DB, RCT, U.S. (Journal of Clinical Psychopharmacology)	Scale for Assessment of Negative Symptoms (SAS) PANSS CGI Case Manager Rating Scale–Plus (CMRS+). Quality of life scale (QLS) Patient Functioning Questionnaire (PFQ)	Mean age 41 yrs 66% male 52% white 37% African descent 3% other		NR/NR/346

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Kinon, 2006a DB, RCT, multicenter (40 US centers)	247 withdrew olanzapine: 112 (55.4%) ziprasidone: 135 (70.3%) ITT analysis	CDSS change from baseline at 8 weeks (olanzapine vs. ziprasidone): -6.4 vs. -6.1; P=0.493, MMRM; P=0.497, LOCF Changes from baseline at 24 weeks (olanzapine vs. ziprasidone): CDSS: -6.0 vs. -4.8; P=0.017, LOCF; P=0.105, MMRM MADRS: -12.1 vs. -9.15; P=0.003, LOCF; P=0.010, MMRM PANSS: -13.5 vs. -8.3; P=0.008, LOCF; P=0.061, MMRM % of patients using benzodiazepines 29.2% vs. 39.0%; P=0.043 GAF improvement over 24 weeks: olanzapine: 6.64 (n=168) ziprasidone: 3.15 (n=158) P=0.017 GAF improvement >/= 5 points: olanzapine: 54.2% ziprasidone: 41.1% percentage difference, 13.0, 95% CI: 12.3 to 23.8
Kinon, 2006b DB, RCT, U.S. (Journal of Clinical Psychopharmacology)	190/21/195-288(varied)	change from baseline SANS score olanzapine -12 quetiapine -9 P= 0.09 PANSS total olanzapine -11.3 quetiapine -7.2 P= 0.151 CGI-S olanzapine -0.5 quetiapine -0.2 P= 0.02 CGI-I (endpoint) olanzapine 3.2 quetiapine 3.8 P< 0.001

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Kinon, 2006a DB, RCT, multicenter (40 US centers)	Treatment-emergent events, electrocardiogram, vital signs, fasting lab analytes, weight, EPS (SAS, Barnes Akathisia Scale, AIMS)	Differences in AEs (olanzapine vs. ziprasidone) Weight gain: 20.3% vs. 5.8%, P<0.001 Increased appetite: 10.4% vs. 4.2%, P=0.021 Peripheral edema: 3.0% vs. 0.0%, P=0.031 Psychosis: 2.5% vs. 7.9%, P=0.020 Decreased appetite: 1.0% vs. 5.3%, P=0.017 Influenza & migraine: 0.0% vs. 2.6%, P=0.026
Kinon, 2006b DB, RCT, U.S. (Journal of Clinical Psychopharmacology)	AEs assessed and also SAS, BAS and AIMs	Olanzapine vs quetiapine (%) Psychosis 2.9 vs.9.7 P = 0.014 Pain 2.3 vs. 7.4 P = 0.044 Anorexia 0 vs. 4.6 P = 0.007 Headache 9.8 vs. 14.3 P = 0.131 Somnolence 24 vs. 22.9 P = 0.899

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Kinon, 2006a DB, RCT, multicenter (40 US centers)	Olanzapine vs. ziprasidone SAS (mean change from baseline): -0.37 vs. -0.03, P=0.037 AIMS: -0.68 vs. -0.34, P=0.001 Barnes Akathisia Scale: -0.12 vs. -0.12, P=0.431 Adjunctive use of anticholinergic agents: 18.8% vs. 21.6%, P=0.530	Total withdrawals: 247 (62.7%) olanzapine: 112 (55.4%) ziprasidone: 135 (70.3%) Withdrawals due to AEs: NR	
Kinon, 2006b DB, RCT, U.S. (Journal of Clinical Psychopharmacology)	The treatment groups did not differ significantly; data=NR	190 withdrawals 96 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Klieser, 1991 Heinrich, 1994 Klieser, 1995 DB, RCT Inpatients	Patients diagnosed with acute, paranoid schizophrenia.	28 day study risperidone(N=20): 4mg/day risperidone(N=19): 8mg/day clozapine(N=20): 400mg/day	≥ 3days	Biperiden, short-acting lorazepam
Kluge, 2007 DB RCT Single center Germany	18 to 65 years old, schizophrenia, schizophreniform, or schizoaffective disorder with a Brief Psychiatric Rating Scale (BPRS0–6) score of 24 or more.	Clozapine 266.7 (77.9) mg n=15 Olanzapine 21.2 (2.5) mg. n=15 6 weeks	2- to 9-day screening and washout period,	Benzodiazepines

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Klieser, 1991 Heinrich, 1994 Klieser, 1995 DB, RCT Inpatients	Association for Methodology and Documentation in Psychiatry (AMDP somatic scale), Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI), Electrocardiogram (ECG), Electroencephalogram (EEG), Extrapyramidal Scale (EPS), complete physical examination, blood samples- taken at 3 days, then weekly. Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI), Simpson and Angus Scale for extrapyramidal side effects (EPS), Association for Methodology and Documentation in Psychiatry (AMDP), reports of adverse events, clinical laboratory assessments, vital signs	Median age: 33 years 52.3% Male Ethnicity NR	100% inpatient with diagnosis of schizophrenia Schizophrenia Diagnosis: Disorganized: 1 Catatonic: 1 Paranoid: 46 Paranoid/residual: 1 Unspecified: 2 Schizoaffective psychosis: 8	NR/NR/59
Kluge, 2007 DB RCT Single center Germany	CGI-S, psychopathology using the BPRS0–6 (total score, positive, negative, anxiety and depression subscales) and abnormal eating behavior was assessed weekly using a standardized binary scale	Mean age 29 yrs 60% male Ethnicity NR	Clozapine vs. Olanzapine BMI 25.4 vs. 24.4 Weight, kg 75.7 vs. 73.5 BPRS 36.6 (8.8) vs. 36.7 (9.9) BPRS positive 9.4 (3.7) vs. 10.2 (3.8) BPRS negative 5.9 (2.1) vs. 7.1 (3.4) BPRS anxiety/depression 10.9 (4.5) vs. 8.7 (4.5) CGI S 4.7 (0.6) vs. 4.5 (0.6)	37/ NR/ NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Klieser, 1991 Heinrich, 1994 Klieser, 1995 DB, RCT Inpatients	31/3/28	Clinical Global Impression at Endpoint (CGI): CGI Rating: very much/much improved: R4: 12 vs R8: 8 vs C: 12 CGI Rating: minimally improved: R4: 3 vs R8: 5 vs C: 4 CGI Rating: minimally worse or deteriorated: R4: 5 vs R8: 6 vs C: 4 BPRS scores : baseline vs week 4 vs endpoint Activity: R4: 10.1 vs 5.1 vs 6.9, R8: 9.5 vs 4.7 vs 7.7, C400: 10.5 vs 5.9 vs 7.7 Anergia: R4: 10.3 vs 6.9 vs 8.7, R8: 10.5 vs 8.7 vs 9.1, C400: 10.5 vs 6.9 vs 8.5 Anxiety/depression: R4: 13.5 vs 7.6 vs 9.7, R8: 12.6 vs 8.3 vs 9.2, C400: 13.9 vs 6.2 vs 8.9 Hostility: R4: 8.2 vs 4.4 vs 4.9, R8: 8.7 vs 3.5 vs 6.1, C400: 9.6 vs 5.7 vs 6.8 Thought disturbances: R4: 13.8 vs 6.3 vs 8.5, R8: 11.3 vs 5.3 vs 9.1, C400: 13 vs 7.1 vs 8.5 Total Score: R4: 55.5 vs 30.3 vs 38.7, R8: 52.6 vs 30.5 vs 41.2, C400: 57.4 vs 31.9 vs 40.3
Kluge, 2007 DB RCT Single center Germany	4/ 0/ 30	Clozapine vs. Olanzapine Endpoint values BPRS 15.9 (13.7) vs. 19.1 (13.8) BPRS positive 3.5 (3.9) vs. 5.1 (4.3) BPRS negative 3.2 (3.7) vs. 3.9 (2.2) BPRS anxiety/depression 5.5 (4.2) vs. 5.1 (4.1) CGI-S 2.5 (1.5) vs. 2.3 (1.2) Binge eating at 6 weeks % 13 vs. 27 Food craving at 6 weeks % 27 vs. 53

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Klieser, 1991 Heinrich, 1994 Klieser, 1995 DB, RCT Inpatients	Physical examination, patient self-report	28;7 Withdrawals due to adverse events: Sleep and vigilance: R4: 14(70%) vs R8: 11(58%) vs C400: 13(65%) Appetite: R4: 7(35%) vs R8: 3(16%) vs C400: 14(70%) Gastro-intestinal: R4: 10(50%) vs R8: 7(37%) vs C400: 15(75%) Cardio-respiratory: R4: 4(20%) vs R8: 5(26%) vs C400: 9(45%) Other vegetative: R4: 2(10%) vs R8: 7(37%) vs C400: 12(60%) Other disturbances: R4: 8(40%) vs R8: 7(37%) vs C400: 11(55%) Neurologic: R4: 6(30%) vs R8: 7(37%) vs C400: 6(30%) % Patients worsened on the AMDP scale: R4: 89% vs R8: 79% vs C400: 85%
Kluge, 2007 DB RCT Single center Germany	Simpson-Angus Scale, AEs, electroencephalograms, vital signs	Clozapine vs. Olanzapine n (%) Salivary hypersecretion 7 (47) vs. 3 (20) P = NS Dizziness 6 (40) vs. 1 (6.7) P = NS Fever* 6 (40) vs. 0 (0) P < 0.01 Fatigue 2 (13) vs. 3 (20) P = NS Constipation 3 (20) vs. 1 (7) P = NS Tachycardia 3 (20) vs. 0 (0) P = NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Klieser, 1991 Heinrich, 1994 Klieser, 1995 DB, RCT Inpatients	Simpson and Angus Rating Scale scores (SAS): Mean change from baseline Gait: R4: 0.2 vs R8: 0.4 vs C400: -0.1; p=NS Arm dropping: R4: 0.2 vs R8: 0.2 vs C400: 0.2; p=NS Shoulder shaking: R4: 0.4 vs R8: 0.1 vs C400: 0.1; p=NS Elbow rigidity: R4: 0.1 vs R8: 0.2 vs C400: 0.2; p=NS Wrist rigidity: R4: 0.1 vs R8: 0.2 vs C400: 0.1; p=NS Leg pendulousness: R4: 0.3 vs R8: 0.2 vs C400: 0.1; p=NS Head dropping: R4: 0.1 vs R8: 0.2 vs C400: 0.1; p=NS Glabella tap: R4: 0.1 vs R8: 0.1 vs C400: 0.0; p=NS Tremor: R4: 0.1 vs R8: 0.1 vs C400: 0.2; p=NS Salivation: R4: 0.0 vs R8: 0.2 vs C400: 0.7; p=0.007 Total score: R4: 0.1 vs R8: 0.2 vs C400: 0.1; p=NS Akathisia: R4: 0.1 vs R8: 0.3 vs C400: 0.0; p=NS	31 total withdrawals 7 due to AEs	
Kluge, 2007 DB RCT Single center Germany	SAS olanzapine, baseline 0.09±0.17 to endpoint 0.03 ± 0.06; clozapine, baseline 0.35+ 0.57 to endpoint 0.14 ± 0.16	7 withdrawal 1 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Knegtering, 2004 Open-label Inpatients and outpatients	Schizophrenia, schizophrenia-related psychotic illness.	N=51 quetiapine(N=25): 200-1200 mg/d risperidone (N=26): 1-6 mg/d	NR	NR
Knegtering, 2006 RCT, open-label naturalistic study Inpatients and outpatients	Schizophrenia who were to be switched to a new antipsychotic for clinical reasons as determined by attending psychiatrists.	olanzapine starting dose 10mg (5-15 mg/day permitted, mean dose: 9.4mg/day) risperidone starting dose 1mg (1-6mg/day permitted; mean dose: 3.4mg/day x 6 weeks	NR	Any antipsychotic before entering the study except depot neuroleptics, olanzapine or risperidone

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Knegtering, 2004 Open-label Inpatients and outpatients	Antipsychotics and Sexual Functioning Questionnaire (ASFQ), Utvalg for Kliniske Undersogelser (UKU), PANSS	Mean age: 70.5% Male	Clinical Diagnoses: Brief psychotic disorder: 3(5.8%) Schizophreniform disorder: 8(15.6%) Schizophrenia: 29(56.8%) Schizoaffective disorder: 2(3.9%) Delusional disorder: 1(1.9%) Psychosis: 7(13.7%)	NR/51
Knegtering, 2006 RCT, open-label naturalistic study Inpatients and outpatients	CGI	Mean age: O: 27.2± 7.2; R 26.0 ±6.3 (range: 19-40) Male:(%) O: (n=25) 80; R: (n=21) 90.5 Ethnicity: NR	Clinical diagnoses per DSM-4: brief psychotic disorder: 2 schizophreniform disorder: 4 schizophrenia: 31 schizoaffective disorder: 1 delusional disorder: 3 psychosis NOS: 5	NR/NR46

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Knegtering, 2004 Open-label Inpatients and outpatients	NR	Patients Reporting Sexual Dysfunction at Endpoint: Q: 4/25(16%) vs R: 12/24(50%); p=0.006 Prolactin levels (Mean + SD) and Sexual Dysfunction: Prolactin: Male: Q: 12.1 + 10.1 vs R: 47.1 + 24.1; P=0.00 Female: Q: 18.0 + 21.5 vs R: 78.1+ 55.4; P=0.001 Decreased libido: Male: Q: 4/19(21%) vs R: 6/15(40%); P=0.12 Female: Q: 0 vs R: 3/10(30%); P=0.07 Decreased erection: Male: Q: 2/15(11%) vs R: 5/15(33%); P=0.05 Decreased vaginal lubrication: Female: Q: 0 vs R: 3/9(38%); P=0.05 Decreased orgasm: Male: Q: 1/16(6%) vs R: 4/15(27%); P=0.05 Female: Q: 4/15(27%) vs R: 3/8(38%); P=0.06 Ejaculation dysfunction: Male: Q: 2/14(14%) vs R: 4/14(29%); P=0.18 Sexual dysfunction: Male: Q: 4/19(21%) vs R: 8/14(57%); P=0.02 Female: Q: 0 vs R: 4/10(40%); P=0.04 PANSS total scores: Q: 5.4+12.3 vs R: 8.4+11.2; P=0.43
Knegtering, 2006 RCT, open-label naturalistic study Inpatients and outpatients	0/0/46	CGI: Both groups were considered effective: (rated as much worse, worse, unchanged, improved, or much improved) . "75% of the pts were rated by MD as being clinically significantly improved (improved and much improved) after 6 weeks." (data now shown) Numerically more R pts were rated as improved vs. O, p=NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Knegtering, 2004 Open-label Inpatients and outpatients	NR	NR
Knegtering, 2006 RCT, open-label naturalistic study Inpatients and outpatients	Prolactin levels measured 6 weeks. Sexual dysfunction: 6 weeks post-randomization by a semi-structured interview using UKU (34) administered by 6 trained physicians.	Sexual severity score: R worse than O; p=0.002 (of the 46 pts who completed the trial, 4 (8.7%) reported sexual dysfunction spontaneously) Semi-structure interview: 14/46 (30.4%) mild or severe sexual dysfunction O: 3/25 (12%) reported sexual dysfunction vs. R: 11/21 (52%) Prolactin: O vs. R; NS Type of sexual dysfunction (%) O (n=25) vs. R (n=21), p Decreased libido: 12 vs. 33.3; NS Decreased orgasm: 0 vs. 19; NS Any sexual dysfunction: 12 vs. 52.4, p =.008 Men only: O (n=20) vs. R (n=19) Prolactin: ng/ml, mean ± SD: 15.9 ±5.3, 41.5 ± 19.5, p=±.001 Type of sexual dysfunction (%) O vs. R , p Decreased erection;) vs. 31.6; p=.04 Decreased libido: 5 vs. 31.6; NS Decreased orgasm: 0 vs. 21.1; NS Ejaculation dysfunction: 0 vs. 16.7, NS Any sexual dysfunction: 6.3 vs. 47.4, p =.01 R experienced more serious problems vs. O pts; p=.003 Women only: 2/7 reported missed period and both had high prolactin levels > 48.6 ng/ml (1 taking olanzapine 10mg/day and other risperidone 6 mg/day)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Knegtering, 2004 Open-label Inpatients and outpatients	NR	NR / NR	
Knegtering, 2006 RCT, open-label naturalistic study Inpatients and outpatients	NR	NR / NR	Baseline sexual dysfunction was not recorded because most of the pts were psychotic and considered too ill at study entry to participate in assessment of sexual function. Prolactin level was not measured at baseline. Medication compliance was not formally assessed.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Krakowski, 2006 DB, RCT, parallel, multicenter Inpatients with persistent June 1999-November 2004, USA Krakowski 2009	Confirmed episode of physical assault directed at another person during the hospitalization and some persistence of aggression, as evidenced by the presence of some other aggressive event, whether physical or verbal or against property.	6 weeks escalation and fixed dose schedule: (mg/day) olanzapine 20 clozapine 500 haloperidol 20 Last 6 weeks (variable-dose): antipsychotic dose was allowed to vary within the following ranges: (mg/day) clozapine 200-800 olanzapine 10-25 haloperidol 10-30 X 12 weeks	1-2 weeks (baseline)	Prestudy antipsychotic meds (adjusted during baseline week to not exceed 750mg/day in chlorpromazine equivalents). Double-blind benztropine or benztropine placebo or a combination of both. Pts assigned to atypical antipsychotics were initially receiving benztropine placebo, but if psychiatrist (unaware of assignment) determined clinically that the pts should be treated for EPS, "benztropine supplements" up to 6mg/d (replace the benztropine placebo) was used. Lorazepam, diphenhydramine, or chloral hydrate open-label prn. Mood stabilizers or antidepressants if taking prestudy.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Krakowski, 2006 DB, RCT, parallel, multicenter Inpatients with persistent June 1999-November 2004, USA Krakowski 2009	Principal measure of Efficacy: MOAS (Modified Overt Aggression Scale)--and the score on the MOAS physical aggression subscale PANSS: at baseline and then weekly during the first month of the study and every other week thereafter. Two independent raters performed assessments at baseline, week 6, and week 12; the average of these 2 raters' assessments was included for the analyses of efficacy together with the single-rater ratings from the other points. Safety measures were performed throughout the study. Weekly WBC counts, ECG and PE done prior to entry and at regular intervals during the study.	Age: Clozapine: 35.1 ±12.3 ; Olanzapine: 35.6 ± 9.4 Male, no (%) : C: 31 (83.8) ; O: 29 (78.4%) Ethnicity: (n, %) C vs. O White: 7 (18.9%); 5 (13.5%) Black: 20 (54.1%); 28 (75.7%) Hispanic: 8 (21.6%); 4 (10.8%) Other: 2 (5.4%); 0	No significant difference in the following: median time of survival, length of hospitalization upon entry with a median length of hospitalization of 48 days; proportion of subjects receiving typical or atypical antipsychotic agents prior to randomization; proportion of subjects receiving other psychotropic medications, including mood stabilizers or antidepressants; total number of physical assaults during the 4-wk period preceding the qualifying physical assault	NR/134/110 (102 pts were enrolled in 1 site; 36 were assigned to haloperidol arm)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Krakowski, 2006 DB, RCT, parallel, multicenter Inpatients with persistent June 1999-November 2004, USA Krakowski 2009	40 (discontinued) C: 13; O 11: H 16 /NR/110 (ITT)	MOAS total score: clozapine: mean, 25.1; median 18; interquartile range, 6-34. olanzapine: mean, 32.7; median, 29; interquartile range, 6-51, (Haldol: not abstracted).(all, p<.001) MOAS physical aggression score: clozapine: mean, 10.3 median 4; interquartile range, 0-16. Olanzapine: mean, 14.1; median, 12; interquartile range, 0-20, (Haldol: not abstracted). ; (all, p<.001 Secondary Analysis: Aggression against property: clozapine: mean, 2.6 ;median 0; interquartile range, 0-2. olanzapine: mean, 2.7; median, 0; interquartile range, 0-4, (Haldol: not abstracted). ; (all p<.001) Secondary Analysis: Verbal aggression: clozapine: mean, 12.2 median 0; interquartile range, 2-15. Olanzapine: mean, 16.0; median, 11; interquartile range, 4-23, (Haldol: not abstracted). ; (all. p<.001) Post-hoc analysis: C vs. O, OR (95% CI for less severe violence)- Total score: 1.30 (1.2-1.4), p<.001 Physical aggression: 1.30 (1.2-1.4); p<.001 Aggression against property:1.10 (0.8-1.5); NS Verbal aggression: 1.32 (1.1-1.5); p<.001 PANSS: (Mean ±SD),p (Haldol not abstracted) Total score C: 2.39 ±14.2; O: 4.83± 9.7; (all p=NS) Positive symptoms: C 1.54± 5; 0: 1.41 ± 3.6; (all p=NS) Negative symptoms: C -0.56 ±4.9; O: 0.72 ± 3.0;(all p=NS) General psychopathology: C 1.43 ± 7.0, O: 2.69 ± 5.5; (all p=NS)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Krakowski, 2006 DB, RCT, parallel, multicenter Inpatients with persistent June 1999-November 2004, USA Krakowski 2009	ESRS performed weekly and a checklist of adverse reactions. Vital signs done twice a day for all pts during the period of clozapine dose escalation (or corresponding period) and once a week thereafter.	"No differences in sedation….among the 3 medication groups" Mean change in body weight from baseline (Kg) Clozapine: 2.36 (7.1), p=0.06 Olanzapine: 3.59 (4.2),p<0.001 Mean change in BMI from baseline: Clozapine:0.76 (2.3), p=0.07 Olanzapine:1.31 (1.6), p<0.001 Mean change in cholesterol from baseline Clozapine:11.4 (38.3)p=0.09 Olanzapine: -1.2 (34.5), p=0.84 Main change in Triglyceride from baseline Clozapine: 56.7 (111.1), p=0.006 Olanzapine:10.7 (56.2), p=0.31 Mean change in Glucose from baseline Clozapine:19.8 (59.6)p=0.7 Olanzapine: -0.1(18.8), p=0.97

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Krakowski, 2006 DB, RCT, parallel, multicenter Inpatients with persistent June 1999-November 2004, USA Krakowski 2009	"No differences in …. and EPS among the 3 medication groups"	40 total withdrawals 8 (C 3; O 1; H 4) due to AEs	Study was conducted on research ward. Overall total MOAS score was computed b y assigning a different weight for each type of aggressive event, using a psychometrically validated method developed by the MOAS authors. Verbal aggression assigned the lowest weight and physical aggression the highest.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Lieberman, 2005 (CATIE Study) Row 1 of 3	Patients age 18-65, DSM-IV criteria for schizophrenia, be appropriate candidates for oral therapy (patients assessment in conjunction with clinician), have adequate decisional capacity to decide to participate.	olanzapine 7.5mg quetiapine 200mg risperidone 1.5mg perphenazine 8mg ziprasidone 40mg The dose of medications was flexible, ranging from one to four capsules daily, and was based on the study doctor's judgment	Overlap in the administration of the antipsychotic agent that patients received before the study entry was permitted for the first four weeks after randomization to allow a gradual transition to study medication	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.
Lieberman, 2005 (CATIE Study) Row 2 of 3 (for results and AEs)				

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Lieberman, 2005 (CATIE Study) Row 1 of 3	Primary outcome measure: -discontinuation of treatment for any cause Secondary outcome -PANSS -CGI -Laboratory measures	Mean age: 40.6 years 26% Female Ethnicity: white 60%; black 35%; Hispanic 12%; 5% other	depression 28% alcohol dependence or alcohol abuse 25% drug dependence or drug abuse 29% obsessive-compulsive disorder 5% other anxiety disorder 14%	NR/NR/1493
Lieberman, 2005 (CATIE Study) Row 2 of 3 (for results and AEs)				

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Lieberman, 2005 (CATIE Study) Row 1 of 3	NR/NR/1460	The time to the discontinuation of treatment for any cause: hazard ratio (95%CI) olanzapine vs quetiapine: 0.63(0.52-0.76) olanzapine vs risperidone: 0.75(0.62-0.90) olanzapine vs perphenazine: 0.78(0.63-0.96), NS after adjustment olanzapine vs ziprasidone: 0.76(0.60-0.97), NS after adjustment quetiapine vs risperidone: 1.19(0.99-1.42) quetiapine vs perphenazine: 1.14(0.93-1.39) quetiapine vs ziprasidone: 1.01(0.81-1.27) risperidone vs perphenazine: 1.00(0.82-1.23) risperidone vs ziprasidone: 0.89(0.71-1.14) perphenazine vs ziprasidone: 0.90(0.70-1.16) The time to the discontinuation of treatment for lack of efficacy: hazard ratio (95%CI) olanzapine vs quetiapine: 0.41(0.29-0.57) olanzapine vs risperidone: 0.45(0.32-0.64) olanzapine vs perphenazine: 0.47(0.31-0.70) olanzapine vs ziprasidone: 0.59(0.37-0.93), NS after adjustment quetiapine vs risperidone: 0.49(NR) quetiapine vs perphenazine: 0.47(NR) quetiapine vs ziprasidone: 0.69(NR) risperidone vs perphenazine: 0.59(NR) risperidone vs ziprasidone: 0.93(NR) perphenazine vs ziprasidone: 0.44(NR)
Lieberman, 2005 (CATIE Study) Row 2 of 3 (for results and AEs)		The time to the discontinuation of treatment owing to intolerability: hazard ratio (95%CI) olanzapine vs quetiapine: 0.84(NR) olanzapine vs risperidone: 0.62(0.41-0.95) olanzapine vs perphenazine: 0.49(NR) olanzapine vs ziprasidone: 0.28(NR) quetiapine vs risperidone: 0.65(0.42-1.00) quetiapine vs perphenazine: 0.97(NR) quetiapine vs ziprasidone: 0.87(NR) risperidone vs perphenazine: 0.60(0.36-0.98) risperidone vs ziprasidone: 0.79(0.46-1.37) perphenazine vs ziprasidone: 0.19(NR) Duration of successful treatment: hazard ratio (95%CI) olanzapine vs quetiapine: 0.53(0.43-0.67) olanzapine vs risperidone: 0.69(0.55-0.87) olanzapine vs perphenazine: 0.73(0.57-0.93) olanzapine vs ziprasidone: 0.75(0.58-0.94) quetiapine vs risperidone: 1.30(1.04-4.63) quetiapine vs perphenazine: 1.28(1.00-1.64) quetiapine vs ziprasidone: 1.06(0.85-1.33) risperidone vs perphenazine: 0.72(NR) risperidone vs ziprasidone: 0.74(NR) perphenazine vs ziprasidone: 0.25(NR) *p=0.004 for the interaction between treatment and time

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Lieberman, 2005 (CATIE Study) Row 1 of 3	AIMS global severity Barnes Akathisia Rating Scale Simpson-Angus Extrapyramidal Signs Scale	olanzapine vs quetiapine vs risperidone vs perphenazine vs ziprasidone, p value Hospitalization for exacerbation of schizophrenia, no(%): 33(11%) vs 68(20%) vs 51(15%) vs 41(16%) vs 33(18%), p<0.001 Hospitalization risk ratio: 0.29 vs 0.66 vs 0.45 vs 0.51 vs 0.57 Any serious adverse events, no(%): 32(10%) vs 32(9%) vs 33(10%) vs 29(11%) vs 19(10%), p=0.47 Any moderate or severe spontaneously reported adverse event, no(%): 122(36%) vs 113(34%) vs 123(36%) vs 79(30%) vs 65(35%), p=0.10 Insomnia: 55(16%) vs 62(18%) vs 83(24%) vs 66(25%) vs 56(30%), p,0.001 Hypersomnia: 104(31%) vs 103(31%) vs 96(28%) vs 74(28%) vs 45(24%), p=0.18 Urinary hesitancy, dry mouth, constipation: 79(24%) vs 105(31%) vs 84(25%) vs 57(22%) vs 37(20%), p,0.001 Decreased sex drive, arousal, ability to reach orgasm: 91(27%) vs 69(20%) vs 91(27%) vs 64(25%) vs 35(19%), p=0.59 Gynecomastia, galactorrhea: 7(2%) vs 6(2%) vs 14(4%) vs 4(2%) vs 6(3%), p=0.15 Menstrual irregularities: 11(12%) vs 5(6%) vs 16(18%) vs 7(11%) vs 8(14%), p=0.17 Incontinence, nocturia: 18(5%) vs 15(4%) vs 25(7%) vs 6(2%) vs 10(5%), p=0.04 Orthostatic faintness: 31(9%) vs 38(11%) vs 37(11%) vs 29(11%) vs 24(13%), p=0.08 Discontinuation of treatment owing to intolerability, no(%) -discontinuation: 62(18%) vs 49(15%) vs 34(10%) vs 40(15%) vs 28(15%), p=0.04 -weight gain or metabolic effects: 31(9%) vs 12(4%) vs 6(2%) vs 3(1%) vs 6(3%), p<0.001 -extrapyramidal effects: 8(2%) vs 10(3%) vs 11(3%) vs 22(8%) vs 7(4%), p=0.002 -sedation: 7(2%) vs 9(3%) vs 3(1%) vs 7(3%) vs 0(0%), p=0.10 -other effects: 16(5%) vs 18(5%) vs 14(4%) vs 8(3%) vs 15(8%), p=0.16
Lieberman, 2005 (CATIE Study) Row 2 of 3 (for results and AEs)		Weight gain >7%: 92(30%) vs 49(16%) vs 42(14%) vs 29(12%) vs 12(7%), p<0.001 Weight change, lb, mean(SE): 9.4(0.9) vs 1.1(0.9) vs 0.8(0.9) vs -2.0(1.1) vs -1.6(1.1), p<0.001 Weight change, lb/month, mean(SE): 2(0.3)vs 0.5(0.2) vs 0.4(0.3) vs -0.2(0.2) vs -0.3(0.3), p<0.001 AIMS global severity score >= 2: 32(14%) vs 30(13%) vs 38(16%) vs 41(17%) vs 18(14%), p=0.23 Barnes Akathisia Rating Scale global score >= 3: 15(5%) vs 16(5%) vs 20(7%) vs 16(7%) vs 14(9%), p=0.24 Simpson-Angus Extrapyramidal Signs Scale mean score >= 1: 23(8%) vs 12(4%) vs 23(8%) vs 15(6%) vs 6(4%), p=0.47 Laboratory values, change from baseline, mean(SE) after adjustment, p value -blood glucose, mg/dl: 13.7(2.5) vs 7.5(2.5) vs 6.6(2.5) vs 5.4(2.8), p=0.59 -glycosylated hemoglobin, %: 0.40(0.07) vs 0.04(0.08) vs 0.07(0.08) vs 0.09(0.09) vs 0.11(0.09), p=0.01 -cholesterol, mg/dl: 9.4(2.4) vs 6.6(2.4) vs -1.3(2.4) vs 1.5(2.7) vs -8.2(3.2), p<0.001 -triglycerides, mg/dl: 40.5(8.9) vs 21.2(9.2) vs -2.4(9.1) vs 9.2(10.1) vs -16.5(12.2), p<0.001 -prolactin, ng/dl: -8.1(1.4) vs -10.6(1.4) vs 13.8(1.4) vs -1.2(1.6) vs -5.6(1.9), p<0.001 Prolonged corrected QT interval, no(%): 0(0%) vs 6(3%) vs 7(3%) vs 2(1%) vs 2(1%), p=0.03

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Lieberman, 2005 (CATIE Study) Row 1 of 3	Olanzapine vs quetiapine vs risperidone vs perphenazine vs ziprasidone, p value Simpson-Angus Extrapyramidal Signs Scale mean score >= 1: 23(8%) vs 12(4%) vs 23(8%) vs 15(6%) vs 6(4%), p=0.47	Olanzapine vs quetiapine vs risperidone vs perphenazine vs ziprasidone, p value Total withdrawals, no(%): 210(64%) vs 269(82%) vs 245(74%) vs 192(75%) vs 145(79%) discontinuation due to intolerability: 62(18%) vs 49(15%) vs 34(10%) vs 40(15%) vs 28(15%), p=0.04	
Lieberman, 2005 (CATIE Study) Row 2 of 3 (for results and AEs)			

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Lieberman, 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008				

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Lieberman, 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008			Meyer 2008 "Change in metabolic.." Olanzapine verus Risperidone versus Quetiapine versus Ziprasidone n=164 vs 147 vs 143 vs 77 Proportion of patients with metabolic syndrome at baseline: 34.8% vs 30.6% vs 37.8% vs 37.7%	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Lieberman, 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008		Patients' decision to discontinue treatment: hazard ratio (95%CI) olanzapine vs quetiapine: 0.56(0.42-0.75) olanzapine vs risperidone: 0.67(0.50-0.90) olanzapine vs perphenazine: 0.70(0.50-0.98) olanzapine vs ziprasidone: 0.63(0.43-0.93) quetiapine vs risperidone: 0.21(NR) quetiapine vs perphenazine: 0.46(NR) quetiapine vs ziprasidone: 0.63(NR) risperidone vs perphenazine: 0.95(NR) risperidone vs ziprasidone: 0.21(NR) perphenazine vs ziprasidone: 0.27(NR) From Meyer 2008 Change in metabolic syndrome: Olanzapine vs Risperidone vs Quetiapine vs Ziprasidone Metabolic Syndrome prevalence at 3 months 43.9% vs 30.6% vs 37.1% vs 29.9% Olanzapine versus Ziprasidone p=0.001 Olanzapine vs quetiapine vs Risperidone vs Ziprasidone 3 months changes from baseline in non fasting triglyceride(mg/dl) Adjusted LSM±SE: 23.4±22.8 vs 54.7±23.5 vs -18.4 ±24.0 vs 0.0 ±32.7, p=0.0009 % of patients reporting paid employment at 18 months: 17% vs 25% vs 23% vs 31%, (Data interpreted from Graph) p=NS Decline in rates of violence at 6 months: 33.9% vs 14.1% vs 25.0%, 24.3% Difference in incidence or severity of TEAE between Olanzapine vs Quetiapone vs Risperidone vs Ziprasidone=NS based on ratign scales for Parkinsonism, Akathisia, Dystonia or tardive Dyskinesia use of antiparkinsonism medications greater with risperidone and lower with quetiapine (P=0.029), and lower rates of discontinuation due to Parkinsonism symptoms were found with quetiapine and ziprasidone (P< 0.05; rates not reported).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Lieberman, 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008		Rates of discontinuation and time to all-cause discontinuation median time in months (illicit drug non users) Olanzapine: 56%, 13.02 mo Quetiapine:81%, 5.02 mo Risperidone: 69%, 5.57 mo Discontinuation rate significantly lower and time to all cause discontinuation significantly longer for olanzapine compared to quetiapine and risperidone Ziprasidone: 77%, 4.34 mo Odds of discontinuation olanzapine vs quetiapine (HR=0.52, CI 0.40 to 0.67, p<0.001) olanzapine vs risperidone (HR=0.70 , CI 0.53 to 0.92, p=0.01) olanzapine vs ziprasidone (HR=0.78, CI 0.56 to 1.08, p=0.13) Quetiapine to risperidone: (HR=1.35; CI 1.05 to 1.73, p=0.021) Rates of medication compliance=NSD between groups. Rates of discontinuation and time to all-cause discontinuation median time in months (illicit drug users) Olanzapine: 74%, 6.75 mo Quetiapine:82%, 4.36 mo Risperidone: 79%, 4.61 mo Ziprasidone: 82%, 3.29 mo, discontinuation rates between olanzapine and other drugs not significantly different. olanzapine vs quetiapine: HR=0.90, CI 0.67 to 1.20, p=0.47 olanzapine vs risperidone: HR=0.93, CI 0.70 to 1.24 olanzapine vs ziprasidone :HR=0.75, CI0.53 to 1.07, p=0.11

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Lieberman, 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C. Meyer 2008 "change in metabolic.. Meyer 2008 "Impact of antipsychotic treatment Resnick 2008 Swanson 2008 Swartz 2008 Miller 2008			

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Lindenmayer, 1998 Open-label Inpatients	Treatment-refractory schizophrenia.	12 week study Mean dose: clozapine: 363.02 mg/day risperidone: 8.95 mg/day	NR	Anticholinergics
Lindenmayer, 2008 DB RCT Multisite, 45 centers in USA, 4 centers in Canada	Inclusion: Men or women aged 18-65 with DSM-IV diagnosis of schizophrenia catatonic, disorganized, paranoid, or undifferentiated; PANSS total score >=60; score of >=4 for at least one of the PANSS items of delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution; a CGI-S score >=4; and a worsening of the patient's condition in the previous 3 weeks. Exclusions: Axis I DSM-IV diagnosis such as mental retardation, or alcohol or substance abuse; hospitalization for schizophrenia for >1 month prior to study; any clinically relevant other diseases; previous treatment resistance to quetiapine; known lack of response to clozapine, use of clozapine for symptom control, or treated with clozapine within 1 month of randomization.	6 treatment groups: Quetiapine XR 300, 600, or 800 mg/day Quetiapine IR at 300 or 600 mg/day Placebo Patients who were screened as outpatients were hospitalized when enrolled and could be discharged on Day 10. Dose initiation phase: Days 1-7.	>=48 hours before randomization; depot antipsychotics discontinued at least 1 dosing interval before randomization.	During days 1-6: lorazepam allowed for agitation. Anticholinergics were discontinued >=48 hours before randomization but allowed for emergent EPS.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Lindenmayer, 1998 Open-label Inpatients	Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions (CGI), neurologic rating scales, plasma drug levels, administered at baseline and endpoint	Mean age: 39.29 years 74.3% Male White: 25.7% African-American: 37.1% Hispanic: 37.1%	100% inpatient Schizophrenia: Disorganized: 5.7% Paranoid: 40% Undifferentiated: 54.3%	NR/NR/35
Lindenmayer, 2008 DB RCT Multisite, 45 centers in USA, 4 centers in Canada	PANSS and CGI-S at randomization, and days 4, 8, 15, 28, and 42. CGI-I at every visit except randomization. Primary endpoint: change in PANSS total score from baseline to Day 42. Other endpoints: PANSS positive, negative, and general psychopathology subscale scores, activation factor score, and depression item score at each visit, and changes from baseline at each visit. PANSS response rate at Day 42 (defined as a decrease of >=30% from baseline); CGI-S score and change from baseline at each visit; CGI-I score at each post-baseline visit.	Mean age 39.1 74.7 % male 49.7% White 37% Black 1.43% Asian 10.7 % Hispanic	80.5% paranoid subtype 17.1% undifferentiated Mean age at first treatment of schizophrenia 23.5 245 with 11 or more previous hospitalizations 30.4% with full response to previous AP. 60.7% with partial response to previous AP 3.6% with poor response to previous AP. 5.0% with no previous exposure to AP. Mean PANSS total score: 90.5 Mean CGI-S: 4.7	Screened NR Eligible NR 532 enrolled

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Lindenmayer, 1998 Open-label Inpatients	3/0/32	Mean PANSS/CGI scores: Clozapine: baseline vs week 6 vs week 12: Positive factor: 17.5 vs 15.7 vs 13.8 Negative factor: 20.6 vs 17.5 vs 15.5 Cognitive factor: 17.2 vs 14.5 vs 13.4 Excitement factor: 9.0 vs 6.7 vs 6.2 Anxiety-depression factor: 8.2 vs 7.1 vs 6.3 CGI Global Severity: 4.8 vs 4.2 vs 3.9 CGI Global Improvement: 3.8 vs 3.3 vs 2.6 Risperidone: baseline vs week 6 vs week 12: Positive factor: 18.5 vs 15.2 vs 15.5 Negative factor: 20.3 vs 18.1 vs 16.1 Cognitive factor: 16.7 vs 14.7 vs 13.4 Excitement factor: 7.5 vs 7.0 vs 6.8 Anxiety-depression factor: 7.4 vs 7.3 vs 5.5 CGI Global Severity: 4.7 vs 4.4 vs 3.9 CGI Global Improvement: 3.6 vs 3.5 vs 3.3
Lindenmayer, 2008 DB RCT Multisite, 45 centers in USA, 4 centers in Canada	310 withdrew 33 lost to followup 48 analyzed	Improvement from baseline in PANSS total score at Day 42, LSM, p-value compared with placebo: Placebo: -5.19 Quetiapine XR 300 mg/day: -5.01; p=NS Quetiapine XR 600 mg/day: -13.01; p=0.033 Quetiapine XR 800 mg/day: -11.17; p=NS Quetiapine IR 300 mg/day: -9.42; p=NS Quetiapine IR 600 mg/day: -6.97; p=NS No significant differences between active treatment groups and placebo on improvement in PANSS positive and negative subscale scores, PANSS response rates at Day 42, or change from baseline in CGI-S score. CGI-I response rate was significantly greater in Quetiapine XR 800 mg/day (35.3%; p<0.05) and Quetiapine IR 300 mg/daY (42.4%; p<0.01) compared with placebo (19.2%). All other treatment groups were not significantly different from placebo. Adherence: 494/498 (99.2%) of patients in the efficacy analysis were adherent to the study medication.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Lindenmayer, 1998 Open-label Inpatients	NR	Seizure: 1, leukopenia: 2, hypertension: 1, tachycardia: 1
Lindenmayer, 2008 DB RCT Multisite, 45 centers in USA, 4 centers in Canada	Body weight, vital signs, and AEs recorded at each visit. Lab measurements and ECG data recorded at screening and Day 42 or final visit. BARS, AIMS, and SAS at baseline and at each visit. Use of anticholinergic medication recorded throughout the study.	AEs in 5 patients led to withdrawal: Orthostatic hypotension: 1 in quetiapine XR 600 mg/day. Grand mal convulsion: 1 in quetiapine IR 600 mg/day, 1 in placebo Psychotic disorder: 1 in quetiapine IR 600 mg/day EPS (dyskinesia and akathisia): 1 in quetiapine IR 600 mg/day Placebo vs Quetiapine XR 300 vs XR 600 vs XR 800 vs IR 300 vs IR 600, % of group: Sedation: 9.5 vs 13.2 vs 20.7 vs 23.6 vs 15.6 vs 22.1 Somnolence: 7.1 vs 7.7 vs 15.2 vs 9.0 vs 13.3 vs 10.5 Dry mouth: 1.2 vs 12.1 vs 14.1 vs 12.4 vs 8.9 vs 8.1 Hypotension: 1.2 vs 8.8 vs 4.3 vs 3.4 vs 4.4 vs 7.0 Dizziness: 2.4 vs 7.7 vs 13.0 vs 9.0 vs 6.7 vs 8.1 Constipation: 0 vs 7.7 vs 7.6 vs 3.4 vs 0 vs 3.5 Diastolic BP decreased: 2.4 vs 7.7 vs 2.2 vs 3.4 vs 3.3 vs 5.8 Tachycardia: 2.4 vs 5.5 vs 8.7 vs 5.6 vs 8.9 vs 11.6 Heart rate increased: 4.8 vs 3.3 vs 10.9 vs 10.1 vs 4.4 vs 10.5 Weight increased: 2.4 vs 2.2 vs 4.3 vs 5.6 vs 6.7 vs 4.7 Blurred vision: 0 vs 0 vs 5.4 vs 1.1 vs 1.1 vs 0 % of patients with >=7% increased in body weight: 1.3 vs 8.0 vs 7.7 vs 3.5 vs 6.8 vs 14.8 Mean change in total cholesterol at Week 6, mg/dL: 0.13 vs 14.62 vs 8.20 vs 14.19 vs 5.72 vs 12.8 Mean change in prolactin (microg/L) at week 6: -6.62 vs -13.47 vs -7.0 vs -12.23 vs -7.86 vs -10.29

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Lindenmayer, 1998 Open-label Inpatients	NR	NR total withdrawals 5 due to AEs	
Lindenmayer, 2008 DB RCT Multisite, 45 centers in USA, 4 centers in Canada	Dyskinesia and akathisia in 1 patient on quetiapine IR 600 mg/day led to withdrawal. Placebo vs Quetiapine XR 300 vs XR 600 vs XR 800 vs IR 300 vs IR 600:, Incidence of EPS-related adverse events, % of group: 4.8 vs 9.9 vs 10.9 vs 12.4 vs 8.9 vs 10.5	310 withdrawals 36 due to AE	Figure 1 states that 36 withdrew due to AE, but narrative describes only 5 of these patients and the AE that led to withdrawal.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
McCue, 2006 RCT, open-label, U.S. Inpatients Funding - NR	Inclusion: 18 years and older of either gender, who were newly admitted to the hospital's psychiatric inpatient service between January 2004 and February 2005, diagnosed with schizophrenia, schizoaffective disorder or schizophreniform disorder Exclusion: Pregnant or lactating women; a medical condition in which pharmacotherapy would prove a significant clinical risk; a clear history of response or lack of response to a particular antipsychotic drug and who, in the judgment of the treating psychiatrist, would best be treated accordingly; a diagnosis of bipolar disorder, major depressive disorder or substance-induced psychotic disorder. .	aripiprazole, mean 21.8 mg, range 10–45; haloperidol, mean 16.0 mg, range 4–30; olanzapine, mean 19.1 mg, range 5–40; quetiapine, mean 652.5 mg, range 50–1200; risperidone, mean 5.2 mg, range 2–9; ziprasidone, mean 151.2 mg, range 40–240. minimum of 3 weeks	None	haloperidol, lorazepam and diphenhydramine for agitation; diphenhydramine for sleep. Benzatropine could also be prescribed for extrapyramidal side-effects; after 2 weeks an antidepressant, mood stabilizer or anxiolytic could be prescribed
McEvoy, 2006 CATIE Phase 2E	Discontinuation of previous phase 1 treatment because of inefficacy.	Open-label clozapine 332.1mg or blinded capsules of olanzapine 23.4mg, quetiapine 642.9mg, or risperidone 4.8mg (mean modal doses)	Overlap in the administration of the antipsychotic agent that patients received before the study entry was permitted for the first four weeks after randomization to allow a gradual transition to study medication	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.
McQuade, 2004 DB, RCT, multicenter Inpatients Meyer 2009	Schizophrenia, in acute relapse, requiring hospitalization, 18 years of age and older, a Positive and Negative Syndrome Scale (PANSS) total score of $\geq$60 and a score of $\geq$4 on a least 2 of the following PANSS items: delusions, hallucinatory behavior, conceptual disorganization, suspiciousness.	N=317 aripiprazole (N=156): 15-30 mg/d olanzapine (N=161): 10-20 mg/d 26 week duration	2 days minimum or 1 dept cycle after the most recent dept antipsychotic injection	lorazepam up to 4mg/day allowed, not within 4 hours of efficacy/safety assessments

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
McCue, 2006 RCT, open-label, U.S. Inpatients Funding - NR	ability to discharge the patient from acute in-patient care and the total score on the Brief Psychiatric Rating Scale. Ratings were made at baseline, weekly up to 3 weeks, and at end-point.	Mean age 37.6 62% male Ethnicity- NR	BPRS total score (mean): 42.3 Length of illness (mean years): 13.2 Diagnosis: Schizophrenia=75.9% Schizoaffective=19.4% Schizophreniform=4.7% Substance misuse (% patients): 35.7	584/NR/364
McEvoy, 2006 CATIE Phase 2E	Primary outcome measure: Time until treatment discontinuation for any reason Secondary outcomes: Time to discontinuation for inadequate therapeutic benefit, intolerable side effects, or patient decision	Mean age=39.7 years 81% male 64% white 33% black/African American 3% all other racial groups	DSM-IV diagnosis present in the past 5 years (% pts): Depression=33% Alcohol dependence/abuse=25% Drug dependence/abuse=24%	1,052/1,052/99 509 (48%) left study from Phase 1 444 (42%) entered Phase 2T
McQuade, 2004 DB, RCT, multicenter Inpatients Meyer 2009	Body weighing, Positive and Negative Syndrome Scale and Clinical Global Impressions-Improvement	Mean Age: 38.4 Male: 72% Ethnicity NR	In-Patient population: 100%	NR/NR/378

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
McCue, 2006 RCT, open-label, U.S. Inpatients Funding - NR	18//NA/319 analyzed	Aripiprazole vs Haloperidol vs Olanzapine vs Quetiapine vs Risperidone vs Ziprasidone Patient outcome, n (%) Effective 34 (64) vs 51 (89) vs 48 (92) vs 32 (64) vs 50 (88) vs 32 (64) Change in BPRS total score: mean (SD.) 12.9 (12.3) vs 16.4 (11.4) vs 14.9 (11.3) vs 14.2 (12.5) vs 15.4 (10.6) vs 14.2 (12.9) Time to 'Effective', days: mean (SD.) 17.6 (10.5) vs 18.6 (10.6) vs 19.5 (13.1) vs 16.8 (8.0) vs 20.4 (13.5) vs 19.5 (8.5)
McEvoy, 2006 CATIE Phase 2E	62 (63%) withdrawn/none lost to fu/90 (91%) included in analysis	<u>Median time until treatment discontinuation for any reason (months)</u> Clozapine=10.5 vs olanzapine=2.7 vs quetiapine=3.3 months vs risperidone=2.8 months Hazard ratios (95% CI) for pair-wise comparisons: Clozapine vs quetiapine=0.39 (0.19, 0.80) Clozapine vs risperidone=0.42 (0.21, 0.86) Clozapine vs olanzapine=0.57 (0.29, 1.16) <u>Discontinuations due to lack of efficacy (% pts)</u> Clozapine=11% vs olanzapine=35% vs quetiapine=43% vs risperidone=43% Hazard ratios (95% CI) for pair-wise comparisons: Clozapine vs olanzapine=0.24 (0.07, 0.78) Clozapine vs quetiapine=0.16 (0.04, 0.54) Clozapine vs risperidone=0.16 (0.05, 0.54) <u>PANSS Total Score Change at 3 months (p-value represents pair-wise comparison to clozapine)</u> Clozapine= -11.7 vs olanzapine= -3.2 (p=0.22) vs quetiapine= 2.5 (p<0.02) vs risperidone= 4.1 (p<0.03) <u>CGI severity change in score at 3 months</u> Clozapine= -0.7 vs olanzapine= 0.1 (p<0.02) vs quetiapine= 0.2 (p=0.003) vs risperidone= 0.0 (p=6.18)
McQuade, 2004 DB, RCT, multicenter Inpatients Meyer 2009	72%/approx.10%/317	At Week 26: % of Patients who had > 7% increase in body weight: O: 37% vs A: 14%; (p<.001) Mean Change in Body Weight from Baseline: O: +4.23 kg (9.40lb) vs A: -1.37 kg (3.04lb); (p<.001) Mean Changes in Fasting Triglyceride Levels: O: +79.4 mg/dL vs A: +6.5 mg/dL; (p<.05) Mean Changes in Fasting HDL Cholesterol Levels: O: -3.39 mg/dL vs A: +3.61 mg/dL; (p<.05) Reduction in Symptoms of Schizophrenia: "No clinically meaningful differences between the aripiprazole and olanzapine groups."

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
McCue, 2006 RCT, open-label, U.S. Inpatients Funding - NR	Physician judgment	Proportion of patients reporting side-effects (week 2: P=0.14; week 3: P=0.72; end-point: P=0.49).
McEvoy, 2006 CATIE Phase 2E	AIMS global severity Barnes Akathisia Rating Scale Simpson-Angus Extrapyramidal Signs Scale Voluntary report of moderate to severe adverse event by systemic inquiry	Clozapine vs olanzapine vs quetiapine vs risperidone (%pts) (p-values are NS unless otherwise specified and come from a test with df=3 comparing all treatment groups) Any AE: 76% vs 74% vs 67% vs 56% Insomnia: 4% vs 16% vs 13% vs 31%, p=0.02 Hypersomnia/sleepiness: 45% vs 32% vs 33% vs 25% Urinary hesitancy/dry mouth/constipation: 20% vs 0 vs 47% vs 6%p=0.002 Sex drive/sexual arousal/sexual orgasm: 33% vs 11% vs 13% vs 25% Gynecomastia/galactorrhea: 2% vs 5% vs 0 vs 0 Menstrual irregularities: 0 for all Incontinence/nocturia: 10% vs 0 vs 13% vs 13% Sialorrhea: 33% vs 11% vs 0 vs 13, p<0.02 Orthostatic faintness: 12% vs 5% vs 27% vs 6% Skin rash: 4% vs 0 vs 7% vs 6% Weight gain from baseline ≥ 7%: 20% vs 13% vs 15% vs 18% Weight change (mean lb): 1.4 vs 6.2 vs 5.1 vs 3.9
McQuade, 2004 DB, RCT, multicenter Inpatients Meyer 2009	Patient self-report	Headache: O: 32% vs A: 23% Insomnia: O: 30% vs A: 32% Anxiety: O: 25% vs A: 20% Somnolence: O: 23% vs A: 8% 6 month data on ethnicity from Meyer 2009 Mean change in body weight from baseline (LSM, SE): A vs O White -1.44 (0.36) vs 3.37 (0.32), p=0.000 Black/Hispanic: 0.99(0.36) vs 4.57 (0.38), p=0.000

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
McCue, 2006 RCT, open-label, U.S. Inpatients Funding - NR	Change in Simpson–Angus Scale ratings from baseline to end-point (F=0.61, .f.=5,307, P=0.69; age as co-variable). Change in score on the Barnes Akathisia Rating Scale from baseline to end-point (F=1.45, df.=5,307, P=0.20; age as co-variable).	18 withdrawals 14 due to AEs	Age was significantly different between groups.
McEvoy, 2006 CATIE Phase 2E	AIMS severity score ≥ 2: 21% vs 21% vs 10% vs 0 Barnes score ≥ 3: 5% vs 0% vs 23% vs 0 Simpson-Angus mean score ≥ 1: 5% vs 13% vs 17% vs 0	See previous results	
McQuade, 2004 DB, RCT, multicenter Inpatients Meyer 2009	EPS-Related Adverse Events: Low: O: 16% vs A: 17% Parkinsonism events: O: 12% vs A: 11% Akathisia: O: 3% vs A: 6%	229 withdrawals Approx. 30% due to adverse events	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Meltzer, 2008 DB RCT United States 3 outpatient centers	Men and women, 18-58 years with schizophrenia or schizoaffective disorder who had failed to respond adequately to prior treatment with other antipsychotic drugs	Olanzapine (25-45 mg/day) n=19 and Clozapine (300-900 mg/day) n=21 for 6 months	2 to 7 day washout	only during washout, haloperidol
Moller, 2008 DB RCT Multinational 74 centers	Outpatients aged 18–65 years with a diagnosis of schizophrenia (including catatonic, disorganized, paranoid and undifferentiated)Patients with a Clinical Global Impressions of Severity of Illness (CGI-S) (National Institutes of Mental Health, 1970) score of 3 or lower were clinically stable	Quetiapine XR n=331 or Quetiapine IR n=166 400, 600 or 800 mg/day 6 weeks	4-week run-in period to confirm clinical stability.	Antidepressants, anxiolytics, hypnotics, mood stabilizers or other psychoactive drugs and drugs that induce or inhibit cytochrome 3A4 enzymes were permitted if treatment had started at least 2 weeks

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Meltzer, 2008 DB RCT United States 3 outpatient centers	PANSS, Schedules for the assessment of positive and negative symptoms, Global Assessment of Functioning, CGI, CGI-S at baseline, 6 weeks and 6 months	Clozapine vs. olanzapine Age 37.2 vs. 36.4 % male 71.4 vs 63.2 % White 57.1 vs. 73.7 % African American 38.1 vs. 15.8 % Asian 0 vs. 10.5 % Other 4.8 vs. 0	Clozapine vs. olanzapine % schizophrenia 80.9 vs. 83.2 % schizoaffective disorder 19.1 vs. 16.8	NR/NR /40
Moller, 2008 DB RCT Multinational 74 centers	CGI-S scale and the PANSS scale were administered at all study visits, and the CGI-I scale day 1, study visits were scheduled for days 7, 14, 21, 28 and 42.	Mean (SD) age (yrs) XR 39.8 (11.4) vs IR 39.9 (10.2) % male 50.9XR vs 57.8 IR Ethnicity (%) White XR 82.7 vs IR 84.9 Black XR 14.2 vs IR 10.8 Asian XR 1.2 vs IR 0.6	PANSS total XR 59.5 (14.3) IR 59.3 (14.7) CGI-S XR 2.6 (0.6) IR 2.7 (0.6)	NR / NR / 630

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Meltzer, 2008 DB RCT United States 3 outpatient centers	24 (60%) withdrawn Clozapine (11 (52.4%)) vs. olanzapine (5 (26.3%)) / NR/ 40	Clozapine vs. olanzapine PANSS total 72.1(3.4) vs. 71.7 (2.8) P = 0.92 PANSS positive 15.1 (1.1) vs. 17.8 (0.9) P = 0.07 PANSS negative 20.9 (1.2) vs. 19.1 (1.0) P = 0.28 GAF 62.4 (2.1) vs. 54.8 (1.8) P = 0.01 CGI 2.6 (0.8) vs. 2.3 (0.6) P = 0.76 CGI-S 3.6 (0.2) vs. 3.6 (0.2) P = 0.78
Moller, 2008 DB RCT Multinational 74 centers	38 9 496	Primary outcome - proportion of patients who discontinued study treatment owing to lack of efficacy or whose PANSS total scores increased by 20% or more from randomization to any visit (MITT population): 9.1% XR; 7.2% IR. The estimated difference MITT population was 1.86% (95% CI –3.78, 6.57; P=0.0431) PANSS score LSM change from baseline (95% CI): Total XR – 3.7 (– 5.2, – 2.3) vs. IR– 4.2 (– 6.0, – 2.5) Positive XR – 0.8 (– 1.2, – 0.4) vs. IR – 0.9 (– 1.4, – 0.4) Negative XR – 1.1 (– 1.5, – 0.6) vs. IR – 1.3 (– 1.8, – 0.8) CGI-I score, % of patients with no change or improvement (95% CI) XR 92.7 (89.4, 95.1) vs. IR 93.4 (88.5, 96.3) CGI-S score, mean change from baseline (SD) XR – 0.0 (0.6) vs. – 0.1 (0.6)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Meltzer, 2008 DB RCT United States 3 outpatient centers	Barnes Akathisia Scale (BAS), Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), weight and BMI	Clozapine vs. olanzapine Weight 204.3 (3.3) vs. 217 (2.9) P = 0.01 BMI 30.6 (0.5) vs. 32.6 (0.4) P = 0.006
Moller, 2008 DB RCT Multinational 74 centers	MEDRA, spontaneously reported AEs and AEs reported after standard questioning were recorded at each visit. Body weight, vital signs, BARS and SAS were also measured at each visit. ECG and laboratory measurements were conducted at randomization and on day 42 (glucose regulation and hematology assessments were also conducted on day 28)	XR vs IR n (%) Dry mouth 14 (4.2) vs. 2 (1.2) Somnolence 13 (3.9) vs. 4 (2.4) Fatigue 7 (2.1) vs. 3 (1.8) Sedation 6 (1.8) vs. 6 (3.6) Constipation 4 (1.2) vs. 3 (1.8) Tremor 3 (0.9) vs. 1 (0.6) Weight decreased 3 (0.9) vs. 0 Decreased appetite 2 (0.6) vs. 0 Dizziness 2 (0.6) vs 3 (1.8) Dysgeusia 2 (0.6) vs. 0 Headache 2 (0.6) vs. 1 (0.6) Increased appetite 2 (0.6) vs. 0 Muscle rigidity 2 (0.6) vs. 0 Psychotic disorder 2 (0.6) vs. 0 Tachycardia 2 (0.6) vs. 1 (0.6) Extrapyramidal disorder 0 vs. 2 (1.2) Insomnia 0 vs. 2 (1.2)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Meltzer, 2008 DB RCT United States 3 outpatient centers	Clozapine vs. olanzapine AIMS total 1.4 (0.7) vs. 2.3 (0.6) P = 0.3 SAS total 2.3 (0.6) vs. 1.6 (0.5) P = 0.4	16 withdrawals 0 due to AEs	
Moller, 2008 DB RCT Multinational 74 centers	SAS scores XR vs. IR Improved 20.7% vs. 21.1% Stayed the same 69.3% vs. 76.5% Worsened 10% vs. 2.4% MedDRA terms of tremor, akathisia, muscle rigidity, dyskinesia, hypokinesia, Parkinsonism, extrapyramidal disorder and restlessness: XR 3.3% and IR 2.4%	38 withdrawals 7 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Mori, 2004 Inpatients	Hoyu Mental Hospital inpatients being treated with typical antipsychotics and antiparkinsonian anticholinergic drugs and with symptoms corresponding to DSM-IV criteria for schizophrenia	N= 77 Final Doses: olanzapine (N=20): 16.5 mg/day perospirone (N=18) 37.3 mg/day quetiapine (N=4): 432.5 mg/day risperidone (N=19): 7.37 mg/day 4 weeks duration	NR	NR
Mullen, 1999 (QUEST sub-group)	Psychosis and schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder (MDD), delusional disorder, Alzheimer's Disease, schizophreniform disorder, vascular dementia, or substance abuse dementia.	quetiapine mean dose at completion: 253.9 mg/d; oral risperidone mean dose at completion: 4.4 mg/d; oral Duration: 4 months	NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Mori, 2004 Inpatients	Digit Span Distractibility Test (DSDT)	Mean age: 59.9 years 50.6% Male	Schizophrenia Diagnoses: Disorganized: 23(29.8%) Paranoid: 10(12.9%) Undifferentiated: 34(44.1%)	NR/NR
Mullen, 1999 (QUEST sub-group)	% change from baseline HAM-D scores (schizoaffective; schizophrenia) CGI PANSS	Mean age: quetiapine 45.1 risperidone 46.2 quetiapine 50.9% male risperidone 54.3 % male Ethnicity NR	Special characteristics: included those > 65 years Diagnosis: bipolar: 83/554;20/175 major depressive disorder: 75/554;26/175 schizoaffective: 158/554;57/175 schizophrenia: 218/554;67/175 all non-mood diagnoses: 316/554;103/17	NR/NR/751 quetiapine 554 risperidone 175

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Mori, 2004 Inpatients	NR/NR/77	Changes in percentages of correct responses in neutral DSDT tests: Mean at baseline vs Mean after switching antipsychotics vs Mean after withdrawal of anticholinergics Olanzapine: 0.32 vs 0.34 vs 0.42 Perospirone: 0.39 vs 0.46 vs 0.44 Quetiapine: 0.43 vs 0.36 vs 0.44 Risperidone: 0.36 vs 0.37 vs 0.43 Changes in percentages of correct responses in distractibility DSDT tests: Mean at baseline vs Mean after switching antipsychotics vs Mean after withdrawal of anticholinergics Olanzapine: 0.35 vs 0.39 vs 0.41 Perospirone: 0.43 vs 0.46 vs 0.47 Quetiapine: 0.42 vs 0.36 vs 0.41 Risperidone: 0.26 vs 0.32 vs 0.39 PANSS totals: Mean at baseline vs Mean after switching antipsychotics vs Mean after withdrawal of anticholinergics Olanzapine: 82.1 vs 73.8 vs 69.4; P<0.0001 Perospirone: 72.4 vs 72.6 vs 77.2; P<0.05 Quetiapine: 78.8 vs 73.7 vs 72.9; P<0.001 Risperidone: 81.2 vs 74.9 vs 71.5; P<0.0001 General psychopathology: Mean at baseline vs Mean after switching antipsychotics vs Mean after withdrawal of anticholinergics Olanzapine: 40.9 vs 37.2 vs 35.0; P<0.0001 Perospirone: 37.1 vs 36.8 vs 39.5; P<0.005 Quetiapine: 38.4 vs 36.2 vs 35.8; P<0.001 Risperidone: 40.0 vs 36.8 vs 35.1; P<0.0001
Mullen, 1999 (QUEST sub-group)	NR	Outcome: % change from baseline Hamilton Rating Scale (depression) scores (schizoaffective; schizophrenia) Quetiapine:–41.6%;–41.6% Risperidone:–34.6%;–31.4% (no significant difference between groups) Quetiapine group had significantly (p= 0.028) greater improvement on Hamilton Rating Scale (depression) than risperidone group Higher percentage in quetiapine group had improvement in CGI at each visit compared with risperidone group No statistically significant differences between groups in PANSS scale

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Mori, 2004 Inpatients	NR	NR
Mullen, 1999 (QUEST sub-group)	EPS checklist Anti-EPS medication Adjusted study medication dose	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Mori, 2004 Inpatients	NR	NR / NR	
Mullen, 1999 (QUEST sub-group)	Extrapyramidal events (EPS checklist) declined in both groups; no significant differences between groups in overall occurrence. Odds of risperidone-treated patient having treatment-emergent EPS requiring adjustment of medication or anti-EPS medication 5.6 times greater than odds of quetiapine-treated patient having similar event ($p< 0.001$). Extrapyramidal symptoms rated as 'at least moderate' (EPS checklist) occurred more frequently at each visit in risperidone participants.	NR / NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Naber, 2001	Diagnosis of schizophrenia was confirmed by experienced clinicians relying on criteria according to DSM-IV	olanzapine(N=36): 12.92 mg, risperidone(N=28): 3.55mg, clozapine(N=36): 194.44mg	NR	No
Naber, 2005 DB, RCT, non-inferiority, multicenter (Germany) Inpatients x 2 weeks and then outpatients (flexible dosing)	DSM-4 schizophrenia, a minimum BPRS score of 24. Documented failure to at least one antipsychotic other than clozapine and olanzapine or had experienced intolerable side effects during these prior antipsychotic treatments. Not pregnant or lactating women. No serious somatic illnesses, including alcohol and/or drug dependency. Not received olanzapine at any time or prior clozapine treatment within the last 3 months.	Olanzapine 5-25 mg/day (mean dose 16.2mg) or clozapine 100-400 mg/day (mean dose 209mg) X 26 weeks, followed by a 2 week taper period. Mean actual duration of treatment: 109 days in olanzapine group and 101 days in clozapine group.	2-9 days	benztropine for agitation (lorazepam up to 8mg/day, temazepam up to 30mg/day, diazepam up to 60mg/day, oxazepam up to 100mg/day); chloral hydrate up to 1500mg/day for insomnia, and biperiden up to 6mg.day for treatment-emergent EPS.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Naber, 2001	SWN (subjective well-being under neuroleptic treatment), a self-rating scale, was being developed and compared with the PANSS; this group of patients was assessed at baseline and right before discharge	Mean age: 34.2 years 54% male Ethnicity: NR	NR	Unclear / unclear / 100
Naber, 2005 DB, RCT, non-inferiority, multicenter (Germany) Inpatients x 2 weeks and then outpatients (flexible dosing)	Primary Efficacy Parameter: SWN (both the 20 item short form and the older 38 item full version were used) Secondary parameters included: MLDL, satisfaction score; PANSS (including PBRS scores (BPRS0-6), CGI at screening and CGI Improvement at each visit. Patient's compliance with meds--qualitatively assessed by investigator at each visit	age, (range): 34.0 ± 10.6 (18-59) male: 69 (61%) Ethnicity: NR	Age at onset of disease years (range): 26.9 ± 7.8 (11-55) Number of previous episodes, (range): 4.5 ± 4.7 (0-30) CGI Severity: Moderately ill: 11%, markedly ill: 53%, severely ill: 35%, most extremely ill. 2% SWN total score: (total score: 20 items) 73.1 ± 20.6; (total score: 38 items): 136.0 ± 37.6	NR/ 122/114

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Naber, 2001	NR/NR/100	Change in PANSS mean scores from admission to discharge: clozapine vs risperidone vs olanzapine Total scores: -25.5 vs -12.56 vs -23.55 Positive scores: -6.77 vs -5.29 vs -8.34 Negative: -6.06 vs -2.74 vs -5.23 Change in mean SWN scores, admission to discharge: clozapine vs risperidone vs olanzapine Total scores: +8.78 vs +8.40 vs +18.97 Mental Functioning: +1.78 vs +0.92 vs +3.77 Social Integration: +1.42 vs +1.34 vs +4.33 Emotional Regulation: +2.00 vs +2.04 vs +3.48 Physical Functioning: +1.58 vs +1.65 vs +4.86 Self-control: +1.6 vs +2.16 vs +2.83
Naber, 2005 DB, RCT, non-inferiority, multicenter (Germany) Inpatients x 2 weeks and then outpatients (flexible dosing)	36/27/43 (completed study)	Efficacy Mean changes, BL to endpoint (LOCF, ITT); Group difference (Olanzapine-clozapine) [95% CI] SWN total score change: (20 item): 3.2 [-4.2*, 10.5]; *p=0.002 SWN total score change (38 items): 8.3 [-5.4; 21.9] MLDL satisfaction change: -0.05 [-0.77; 0.67] PANSS total score change: -2.4 [-13.7; -8.4] BPRSO-6 total change:-2.8 [-9.7; -4.2] CGI Severity scores improvement: O 1.4 ± 1.2 vs. C: 1.3 ±1.5

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Naber, 2001	N/A	NR
Naber, 2005 DB, RCT, non-inferiority, multicenter (Germany) Inpatients x 2 weeks and then outpatients (flexible dosing)	Spontaneously reported, Simpson-Angus Scale; routine hematological. clinical laboratory values and vital signs at each visit.	AE possibly or probably related to study drug (spontaneously reported): C 75% vs. O 47%, RR 1.60 (95% CI: 1.26; 2.02) Proportion of patients with any AE: C 91% vs. O 77% RR 1.18 (95% CI: 1.04; 1.34) C> O: dizziness 13% vs. 2%; Increased salivation:18% vs. 0%; constipation: 21% vs. 0%; respectively O> C: Anxiety: 12% vs. 2% Mean Body weight gain (kg): C> O : 5.0 ± 6.8 vs. 3.5± 5.9, respectively Marked weight gain by at least 7% of body weight: C> O; 52% vs. 34% BL BMI < 23 kg/m2--weight gain was most pronounced C > O: 8.2 ± 8.1 vs. 9.0 ±8.9 BL BMI > 27 kg/m2: weight gain was less although still C> O 1.7± 2.4 vs. 3.5 ± 7.2 ECGs: unchanged in majority of pts (O 81%, C 88%)-No serious ECG changes reported. A prolongation of QT-time was reported for one C pt. Blood glucose remained within normal range in all but one C pt who had elevated non-fasting blood glucose levels CGI Therapeutic Index: O > C (mean index: Olanzapine: 2.17 ± 1.22, clozapine 1.63 ± 1.14). CGI Therapeutic Effect ratings were similar in both groups CGI Side Effects: no or no significant impairment by SE in 92% of olanzapine-treated pts vs. 79% clozapine group.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Naber, 2001	NR	NR / NR	There were two groups of patients, one group n=212 and was divided into typicals vs atypicals. The second group was n=100, and was divided between clozapine, risperidone, and olanzapine. It was unclear if the two groups were the same. Olanzapine and risperidone pts were pseudo-randomized; clozapine was given because of insufficient antipsychotic treatment or severe motor symptoms under previous medications. Olanzapine pts were significantly younger than risperidone.
Naber, 2005 DB, RCT, non-inferiority, multicenter (Germany) Inpatients x 2 weeks and then outpatients (flexible dosing)	Simpson Angus Scale improved in both treatment groups: mean total scores decreased: O 2.7 ± 4.8 points with (n=50) and 2.1 ± 4.5 points in C group (n=54) (data not shown). Concomitant antiparkinsonian medications was used in 12% O pts (7/57), 5% C pts (3/57)	71 total withdrawals 12 due to AEs	Recruitment problems. Overall retention rates were 69% after 6 weeks, and 34% at 26 weeks.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Naber, 2005 DB, RCT Inpatients and outpatients	DSM-IV and ICD-10 criteria for schizophrenia, predominantly primary negative PANSS symptoms (negative subscale score ≥21 ; at least 1 pt greater than positive subscale score)	n=44 Risperidone (n=22): days 1-2: 2 mg/day; days 3-5: 4 mg/day; days 6-7: 6 mg/day. Dose up to 8 gm/day allowed after day 7. Quetiapine (n=22): day 1: 50 mg; day 2: 100 mg; titrated up to 600 mg up to day 7. Dose up to 800 mg allowed after day 7.	2 days	lorazepam (≤4 mg/day) zopiclone (≤ 15 mg/day) biperiden hydrochloride (≤8 mg/day)
Newcomer, 2008 DB RCT Multinational Multicenter	Males and females, 18 to 65 yrs w/ schizophrenia or schizoaffective disorder on olanzapine for 1 to 24 months, BMI 27 or more, CGI-S 4 or less.	Aripiprazole 10-30 mg/day n=88 Olanzapine 10-20 mg/day n=85 for 16 weeks	No - 2 week cross titration for aripiprazole	Stable statins, antidepressants (except fluoxetine and paroxetine) benzodiazepines/anxiolytics, mood stabilizers, anti-convulsants, sleeping agents, propranolol and other B-adrenergic blockers
Newcomer, 2009 Open label RCT Multinational, multicenter (58)	Inclusion: Male and female ; age 18-65 yrs; schizophrenia; no prior treatment or had shown inadequate response Exclusion: previous treatment with study agents, clozapine, chlorpromazine, valproic acid, lithium or antidepressants, agents that effect insulin sensitivity, diagnosis of diabetes, pregnancy, other Axis I disorders, clinically relevant disease or depot antipsychotic within 1 dosing interval	Quetiapine vs. Olanzapine vs. Risperidone Mean daily doses 607.0 mg vs. 15.2 mg vs. 5.2 mg 24 weeks	5 day crossover	Benzodiazepines and anticholigenerics

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Naber, 2005 DB, RCT Inpatients and outpatients	Weekly assessments using PANSS, SANS, CGI scale and Simpson-Angus Scale (SAS)	Mean age: 35 yrs (SD 11.6) 61% male Ethnicity NR	PANSS total mean score: 100.6 (SD 16.7) SANS total mean score: 59.2 (SD 20.9) SAS mean score: 0.35 (SD 1.2)	NR/22/22
Newcomer, 2008 DB RCT Multinational Multicenter	Weight change at week 16 Assessments baseline then every 2 weeks starting at week 4	Mean age 39.2 yrs 64.2% male 68.2% Caucasian 24.3% black 2.3% Asian 0.6% Pacific Islander 4.6% other	76.9% schizophrenia 23.1% schizoaffective disorder Mean BMI 32.3	NR/NR/244
Newcomer, 2009 Open label RCT Multinational, multicenter (58)	Oral glucose tolerance test (OGTT) at baseline and 24 weeks, hyperglycemia, changes in body weight, lipid parameters, , CGI-I and CGI-S	Mean age 39 yrs 90% male 73% white	BMI 25 kg/m 75% paranoid	NR/NR/574

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Naber, 2005 DB, RCT Inpatients and outpatients	risperidone 2/0/efficacy NR; safety 22 quetiapine: 4/2/efficacy NR; safety 22	Mean change from baseline at week 12: PANSS total: R -29 vs Q -30 PANSS negative subscale: R -7 vs Q -11 PANSS positive subscale: R -8 vs Q -4 PANSS general psychopathy: R -15 vs Q -16 (all PANSS data interpolated from graph) No SS differences b/t drugs in PANSS subscales SANS total: R -15.5 vs Q -23 SANS affective blunting: R -4 vs Q -6.5 SANS alogia: R -2 vs Q -5; p=0.065 SANS avolition/apathy: R -4.75 vs Q -5.1 SANS anhedonia/asociality: R -4.9 v Q 5.2 SANS disturbance of attention: R -3 vs Q -3.1 (all SANS data interpolated from graph) No SS differences b/t drugs in SANS subscales CGI: R 1.5 (SD 1.6) v Q 1.7 (SD 1.4); p=0.767
Newcomer, 2008 DB RCT Multinational Multicenter	54/0/173	Change in weight at 16 weeks aripiprazole -1.8 kg versus olanzapine +1.41 kg; p < .001. CGI-I endpoint scores olanzapine (mean +/- SE = 3.09 +/- 0.16) versus aripiprazole (mean +/- SE = 3.74 +/- 0.15; p < .001),
Newcomer, 2009 Open label RCT Multinational, multicenter (58)	121/16/395 (those that had measurements at baseline and week 20 or later)	Quetiapine vs. Olanzapine vs. Risperidone CGI-S $\leq$ 3 (%) 70.2 vs. 75.7 vs. 74.3 CGI-I much and vey much improved (%) 57.7 vs. 63.9 vs 55.6 Mean weight change (kg) +3.7 vs. +4.6 vs. +3.6 Mean change in AUC 0-2 hour glucose 9.1 vs. 21.9 vs. 18.8

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Naber, 2005 DB, RCT Inpatients and outpatients	Physical examination	Weight gain: R 1.72 (SD 3.57) kg v Q 2.93 (SD 4.02); p=0.296 Cold: R 14 (8.2%) v Q 3 (13.6%)' p=0.680 Headache: 7 (31.8%) v Q 6 (27.3%); p=0.741 Tiredness: R 5 (22.7%) v Q 17 (77.3%); p<0.001 Insomnia: R 5 (22.7%) vs Q 6 (27.3%); p=0.728 Dizziness: R 6 (27.3%) vs Q 6 (27.3%); p=1.000 Nausea: R 2 (9.1%) vs Q 4 (18.2%); p=0.660 Intermediate (6 wk) serum measurements revealed a SS difference in prolactin levels (R 100 ug/L v Q -18 ug/L; p<0.001) and estrogen (R -21 ug/L v Q 12 ug/L; p<0.01). SS differences in testosterone and SHBG also reported (p<0.05) although graphical data impossible to interpolate (see Fig. 3 in paper)
Newcomer, 2008 DB RCT Multinational Multicenter	Physician assessment at visits, lab values, SAS and AIMs	Aripiprazole vs. olanzapine n(%) Any AE 56 (63.3) vs. 45 (53.6) Nausea 6 (6.8) vs. 1 (1.2) Weight increase 4 (4.5) vs. 5 (6.0) Headache 8 (9.1) vs. 3 (3.6) Insomnia 19 (21.6) vs. 9 (10.7)
Newcomer, 2009 Open label RCT Multinational, multicenter (58)	SAS, BAS and reported AEs and labs	Quetiapine vs. Olanzapine vs. Risperidone % AEs 59.8 vs 47.0 vs. 67.4 Serious AEs 10.1 vs. 2.4 vs. 7.6 Insomnia 6.5 vs. 4.2 vs. 14.5 Somnolence 10.1 vs. 3.6 vs. 4.7 Akathisia 1.2 vs. 1.8 vs. 12.8 Schizophrenia 7.1 vs. 1.2 vs. 4.7 Sedation 6.5 vs. 3.0 vs. 2.9 Dizziness 5.3 vs. 0 vs. 3.5

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Naber, 2005 DB, RCT Inpatients and outpatients	Akathisia: R 8 (36.4%) v Q 0; p=0.006 Parkinsonism: R 8 (36.4%) v Q 0; p=0.006 Use of anticholinergic medication: R 9 (40.9%) v Q 2 (9.1%); p=0.037	19 total withdrawals 3 due to AEs	
Newcomer, 2008 DB RCT Multinational Multicenter	Mean change from baseline Aripiprazole vs. olanzapine SAS -0.21 vs. -0.18 P = 0.822 AIMs -0.05 vs. -0.02 P = 0.914	54 withdrawals 15 due to AEs	
Newcomer, 2009 Open label RCT Multinational, multicenter (58)	Quetiapine vs. Olanzapine vs. Risperidone % Extrapyramidal disorder 1.8 vs. 1.8 vs. 24.4	121 withdrawals 34 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Potkin 2007 DB RCT 21 sites United States Inpatient for first 3 weeks	More than 18 yrs old with schizophrenia CGI-S of 4 or more, PANSS 60 or more, 2 items on PANSS-P of 4 or more.	Asenapine 5 mg bid it n= 58 Risperidone 3 mg bid it n=56 Placebo it n=60 6 weeks	3 to 7 day washout	Yes- zolpidem, zaleplon, chloral hydrate, benzodiazepines, lorazepam, anticholinergic agents
Potkin, 2003b DB, RCT, placebo-controlled, parallel, multicenter Inpatients	Acute, psychosis in patients diagnosed with schizophrenia and schizoaffective disorder Exclusion criteria: psychiatric disorder other than schizophrenia, schizoaffective disorder requiring pharmacotherapy, history of violence, recent history of suicide ideation/attempts, clinically significant neurological abnormality other than tardive dyskinesia or EPS, current diagnosis of psychoactive substance dependence, history of alcohol/drug abuse, treatment with an investigational study drug within 4 weeks before washout, acute/unstable medical condition	aripiprazole: 20 mg/day:(N=101) aripiprazole: 30 mg/day:(N=101) risperidone: 6 mg/day:(N=99) placebo:(N=103)	7 days	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Potkin 2007 DB RCT 21 sites United States Inpatient for first 3 weeks	Improvement from baseline in Positive and Negative Syndrome Scale (PANSS) total score. Secondary outcomes included changes in Clinical Global Impressions-Severity of Illness (CGI-S) score and scores on PANSS positive, negative, and general psychopathology subscales	Asenapine vs. placebo vs. risperidone Age 38 vs. 42 vs. 43 % men 78 vs. 79 vs. 61 % White 42 vs. 32 vs. 42 % Black 47 vs. 52 vs. 44 % Other 10 vs. 16 vs. 14	Asenapine vs. placebo vs. risperidone Type of schizophrenia Paranoid 85% vs. 97% vs. 85% Disorganized 2% 0 vs. 5% Undifferentiated 12% vs. 2% vs. 7% Not specified or obtained 2% vs. 2% vs. 3% Baseline PANSS 96.5 vs. 92.4 vs. 92.2	NR / NR / NR
Potkin, 2003b DB, RCT, placebo-controlled, parallel, multicenter Inpatients	Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression scores (CGI), effects on weight, prolactin, corrected QT interval, Simpson-Angus Scale (SAS), Barnes Akathisia Rating Scale (BAS), Abnormal Involuntary Movements Scale (AIMS)	Mean age: 38.9 years 70% Male Ethnicity NR	100% inpatient	NR/NR/404

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Potkin 2007 DB RCT 21 sites United States Inpatient for first 3 weeks	107 / NR / 180	Asenapine vs. placebo vs. risperidone Mean changes from baseline PANSS -15.9 vs. -5.3 vs. -10.9 Asenapine vs. placebo P < 0.005, risperidone vs. placebo P = NS CGI-S -0.74 vs. -0.28 vs. -0.75 Asenapine or risperidone vs. placebo P < 0.01. risperidone vs. placebo P < 0.005 PANSS-P -5.5 vs. -2.5 vs. -5.1 Asenapine vs. placebo P = 0.01. risperidone vs. placebo P < 0.05 PANSS-N -3.2 vs. -0.6 vs. -1.05 Asenapine vs. placebo P = 0.01, risperidone vs. placebo P = NS
Potkin, 2003b DB, RCT, placebo-controlled, parallel, multicenter Inpatients	162/0/242	PANSS score: P-value=drug vs placebo Total: A20: -14.5 (p=.001) vs A30: -13.9 (p=.003) vs R6: -15.7 (p<.001) vs placebo: -5.0 BPRS score: A20: -3.5 (p=.004) vs A30: -3.3 (p=.01) vs R6: -3.9 (p<.001) vs placebo: -1.7 CGI-score: A20: -0.2 (p=.03) vs A30: -0.6 (p=.006) vs R6: -0.7 (p<.001) vs placebo: -0.2 Body weight: Mean increase in body weight from baseline to endpoint: A20: 1.2 kg vs A30: 0.8 kg vs R6: 1.5 kg vs placebo: -0.3 kg Serum Prolactin Levels: Mean changes in serum prolactin levels from baseline to endpoint: A20: -6.6 ng/mL vs A30: -6.4 ng/mL vs R6: 47.9 ng/mL vs placebo: 0.1 ng/mL

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Potkin 2007 DB RCT 21 sites United States Inpatient for first 3 weeks	Labs and ECG at baseline and then weekly, blood pressure and heart rate twice daily, temperature and respiration once daily. Adverse events recorded weekly	Asenapine vs. placebo vs. risperidone % Experienced one or more AEs 83 vs. 79 vs. 90 Insomnia 19 vs. 13 vs. 22 Somnolence19 vs. 13 vs. 15 Nausea 19 vs. 13 vs. 12 Anxiety 17 vs. 15 vs. 15 Agitation 15 vs. 24 vs. 19 Headache 14 vs. 27 vs. 22 Vomiting 14 vs. 11 vs. 5 Constipation 10 vs. 10 vs. 7 Psychosis 10 vs. 6 vs. 7 Dizziness 8 vs. 15 vs. 7 Dyspepsia 7 vs. 8 vs. 12 URTI 7 vs. 5 vs. 10 Pain 5 vs. 6 vs. 10 Fatigue 3 vs. 6 vs. 10 Hypertonia 0 vs. 3 vs. 12 Greater than 7% weight gain 4.3 vs. 1.9 vs. 17.0
Potkin, 2003b DB, RCT, placebo-controlled, parallel, multicenter Inpatients	Medical examination, patient self-report	Whole body: A20: 58% vs A30: 61% vs R6:53% vs placebo: 59% Cardiovascular system: A20: 1% vs A30: 7% vs R6: 15% vs placebo: 1% Digestive System: A20: 65% vs A30: 52% vs R6: 66% vs placebo: 53% Musculoskeletal System: A20: 6% vs A30: 6% vs R6: 7% vs placebo: 5% Respiratory System: A20: 9% vs A30: 17% vs R6: 22% vs placebo: 8% Skin and appendages: A20: 7% vs A30: 11% vs R6: 8% vs placebo: 7% Blurred vision: A20: 3% vs A30: 5% vs R6: 8% vs placebo: 1% Urogenital System: A20: 1% vs A30: 4% vs R6: 1% vs placebo: 3%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Potkin 2007 DB RCT 21 sites United States Inpatient for first 3 weeks	Asenapine vs. placebo vs. risperidone Mean change from baseline BAS -0.21 vs. 0.25 vs. 0.14 SAS -0.32 vs. -0.24 vs. 0.05 AIMS 0.04 vs. 0.46 vs. -0.02	Asenapine vs. placebo vs. risperidone 107 (59%) (54% vs. 58% vs. 66%) withdrawals 17 (9.4%) (10.2% vs. 6.8% vs. 11.3%) due to AEs	
Potkin, 2003b DB, RCT, placebo-controlled, parallel, multicenter Inpatients	Incidence of EPS-related adverse events: A20: 32 vs A30: 31% vs R6: 31% vs placebo: 20% Mean change in Simpson-Angus Scale scores from baseline to endpoint: A20: -0.16 vs A30: -0.09 vs R6: -0.18 vs placebo: -0.29 Mean change in Barnes Akathisia Rating Scale Global Scores from baseline to endpoint: A20: 0.15 vs A30: 0.18 vs R6: 0.14 vs placebo: 0.11 Mean change in Abnormal Involuntary Movement Scale scores from baseline to endpoint: A20: -0.27 vs A30: -0.5 vs R6: -0.6 (p=.03 against placebo) vs placebo: 0.1	162 total withdrawals 44 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Potkin, 2006 DB, RCT Rupnow 2007	18-64 years of age; DSM-IV diagnosis of schizophrenia (paranoid, disorganized, or undifferentiated type) or schizoaffective disorder confirmed by M.I.N.I.-Plus; experiencing acute exacerbation of their illness of recent onset (within 4 wks) with prominent troublesome symptoms requiring hospitalization; score >/= 4 on at least two of the following items on the PANSS: Hostility, Excitement, Tension, Uncooperativeness, and Poor Impulse Control, and a total score on these 5 items >/= 17 Exclusion criteria: any Axis I diagnosis, except abuse/dependence disorders; an Axis II diagnosis of mental retardation or borderline personality disorder; treatment-resistant schizophrenia; imminent risk for self harm; having received a depot antipsychotic within one dosing cycle prior to baseline; having received risperidone or quetiapine within 7 days prior to baseline; known allergy or sensitivity to either drugs; evidence of a clinically significant or unstable disease, including a thyroid disorder not stabilized for at least 3 months	Risperidone (n=153): titrated from 1 mg/d to target dose 4 mg/d (</= 70 kg) or 6 mg/d (> 70 kg) by day 5. Quetiapine (n=156): titrated from 50 mg/d to target dose of 400 mg/d (</= 70 kg) or 600 mg/d (>70 kg). Placebo (n=73). After Day 5, patients maintained on same dose except that investigators were able to increase dose of quetiapine to 600 mg/d (</= 70 kg) or 800 mg/d (>70 kg) on Day 8. Mean (SD) doses at the additive therapy baseline: Risperidone: 4.7 (0.9) mg/day Quetiapine: 579.0 (128.9) mg/day	Not reported	Use of other psychotropic medications prohibited during monotherapy phase (Days 1-14); however, short-acting, non-benzodiazepine hypnotics (e.g., zolpidem, zaleplon, zopiclone) for treating insomnia, and injectable lorazepam, sodium Amytal, or midazolam for treating agitation or restlessness permitted as needed. After Day 14, investigator could prescribe any psychotropic medication deemed necessary, except specifically prohibited medications (drugs known to interact with the cytochrome P450 isoenzymes CYP2D6 and CYP3A4, and drugs with potential thyroid toxicity); benztropine mesylate or equivalent treatment for movement disorders permitted as needed

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Potkin, 2006 DB, RCT Rupnow 2007	PANSS, CGI-S, CGI-C at baseline and Days 3, 5, 7, 9, 14, 21, 28 and 42 HAM-D-17 at baseline and Days 7, 14, 28 and 42 RDQ rated at Days 3, 5, 7, 14 and 21 MSQ	risperidone vs. quetiapine vs. placebo Mean age (SD): 34.7 (9.6) vs. 34.2 (9.8) vs. 36.1 (9.8) % male: 69% vs. 64% vs. 63% % white: 26% vs. 25% vs. 23% % Hispanic: 0.65% vs. 2% vs. 1% % Black: 14% vs. 13% vs. 15% % Asian: 59% vs. 60% vs. 60% Other: 0 vs. 0.64% vs. 0	risperidone vs. quetiapine vs. placebo Schizophrenia: 92% vs. 93% vs. 90% Schizoaffective disorder: 8% vs. 7% vs. 10% Days since onset of symptoms Mean (SD): 15.3 (6.6) vs. 15.6 (7.0) vs. 16.6 (6.9) Mean PANSS scores: Total: 95.0 (18.0) vs. 97.3 (19.1) vs. 94.3 (18.2) Total of 5 items for inclusion: 20.6 (2.7) vs. 20.7 (2.7) vs. 20.9 (2.6) Mean CGI-S: 5.4 (0.5) vs. 5.4 (0.5) vs. 5.4 (0.6)	400/382/382

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Potkin, 2006 DB, RCT Rupnow 2007	Monotherapy phase (Days 1-14) ITT population: 379 Safety population: 382	Monotherapy Phase Endpoint risperidone vs. quetiapine vs. placebo (p-values risperidone vs. quetiapine): PANSS Total: -27.7 (1.5) vs. -20.5 (1.5) vs. -20.2 (2.0) ; P<0.01 Total of 5 items for inclusion: -9.4 (0.4) vs. -7.8 (0.4) vs. -6.9 (0.6); P<0.01 >/= 30% improvement [number (%) of subjects achieving this level of improvement: 76 (50%) vs. 56 (36%) vs. 26 (37%); P<0.01 PANSS-Marder Factors (LS mean change from baseline value): Positive symptoms: -8.7 (0.5) vs. -5.9 (0.5) vs. -5.3 (0.7); P<0.01 Negative symptoms: -4.0 (0.4) vs. -2.5 (0.4) vs. -3.5 (0.6); P<0.01 Disorganized thoughts: -4.1 (0.4) vs. -2.6 (0.4) vs. -3.0 (0.5); P<0.01 Hostility/excitement: -7.9 (0.4) vs. -6.5 (0.3) vs. -5.9 (0.5); P<0.01 Anxiety/depression: -3.1 (0.2) vs. -2.8 (0.2) vs. -2.6 (0.3) CGI: Mean change CGI-S: -1.8 (0.1) vs. -1.3 (0.1) vs. -1.1 (0.1); P<0.01 Mean (SE) CGI-C: 2.4 (0.1) vs. 2.9 (0.1) vs. 2.9 (0.1); P<0.01 Responders: 68 (45%) vs. 43 (28%) vs. 17 (24%); P<0.01 HAM-D-17: -5.6 (0.4) vs. -5.0 (0.4) vs. -4.4 (0.5); P=NR MSQ, mean (S.E.): 5.2 (0.1) vs. 4.7 (0.1) vs. 4.5 (0.2); P<0.01 RDQ yes: 84 (56%) vs. 59 (38%) vs. 22 (32%); P<0.01 Results from the 28 day additive therapy phase: Risperidone vs Quetiapine (Rupnow 2007) Mean (SD) change in PANSS total score: -34.5 (1.6) vs -30.9 (1.6), p=NS % with ≥30% improvement: 68% vs 62%, p=NS Mean(SD) change in CGI severity: -2.3 (0.1) vs -2.0 (0.1), p<0.05 Additional psychotropics received: 36% vs 53%, p<0.001 Antipsychotics: 33% vs 53% (risperidone vs quetiapine vs placebo p<0.01) Antidepressants: 5% vs 1% mood stabilizers: 2% vs 2% Relative risk quetiapine vs risperidone of antipsychotic polypharmacy: 1.90 (p=0.001; 95% CI 1.29-2.80)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Potkin, 2006 DB, RCT Rupnow 2007	Monitored throughout study and reported at each study visit Parkinsonism, akathisia, and dyskinesia rated using SAS, BAS, and AIMS, respectively	Monotherapy Phase (risperidone vs. quetiapine vs. placebo): At least one TEAE: 100 (65%) vs. 97 (62%) vs. 44 (60%) Insomnia: 29 (19%) vs. 22 (14%) vs. 17 (23%) Headache: 22 (14%) vs. 18 (12%) vs. 10 (14%) Sedation: 10 (7%) vs. 15 (10%) vs. 5 (7%) Somnolence: 4 (3%) vs, 16 (10%) vs. 2 (3%) Dizziness: 9 (6%) vs. 16 (10%) vs. 3 (4%) Cogwheel rigidity: 11 (7%) vs. 5 (3%) vs. 1 (1%) Akathisia: 11 (7%) vs. 1 (<1%) vs. 1 (1%) Constipation: 8 (5%) vs. 14 (9%) vs. 2 (3%) AE from the 28 day additive therapy phase: Risperidone vs Quetiapine (Rupnow 2007) Headache: 6% vs 4% Cogwheel rigidity: 5% vs 3% weight gain: 5% vs 3% tremor: 5% vs 4%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Potkin, 2006 DB, RCT Rupnow 2007	Monotherapy Phase (risperidone vs. quetiapine vs. placebo): AIMS total score (mean change from baseline): 0.3 (0.2) vs. -0.1 (0.2) vs. -0.1 (0.3) SAS total score (mean change from baseline): 0.8 (0.2) vs. -0.1 (0.2) vs. -0.1 (0.3); P<0.01 BAS-Global Severity of Akathisia, Change from baseline [N (%)]: Worsened: 22 (15) vs. 10 (7%) vs. 5 (8%) Unchanged: 114 (78%) vs. 115 (79%) vs. 51 (77%) Improved: 10 (7%) vs. 20 (14%) vs. 10 (15%)	Risperidone vs. quetiapine vs. placebo 14 vs. 24 vs. 13 Withdrawals due to AEs not reported for monotherapy phase (Days 1-14)	All results are for monotherapy phase (2 wks), not additive therapy phase, per Sujata's instructions.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Purdon, 2000 David, 1999 Jones, 1998 DB, RCT, multicenter (Canada)	Schizophrenia; 'early phase'– first 5 years of illness, PANSS < 90	Olanzapine: 5–20 mg/day; Risperidone: 4–10 mg/day; Haloperidol: 5–20 mg/day; Duration: 54 weeks.	1 week	No other antipsychotics, but other meds allowed as needed
QUEST; Mullen, 2001	Psychosis and: schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder (MDD), delusional disorder, Alzheimer's Disease, schizophreniform disorder, vascular dementia, or substance abuse dementia	Quetiapine 50-800 mg/d in divided doses (maximum mean dose=329 mg/d) Risperidone 1-3 mg/d in divided doses (maximum mean dose=5 mg/d at day 64, and 4.65 by day 112)	NR	Any mood stabilizers or antidepressants prescribed must have been at a stable dose for at least 2 weeks before randomization

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Purdon, 2000 David, 1999 Jones, 1998 DB, RCT, multicenter (Canada)	Leaving study early; Mental state: PANSS, Cognitive function: GCIS, neuropsychological test battery, QOL: QLS, SF-36, and resource utilization Symptoms assessed weekly x 6 weeks, then monthly Cognitive assessments at baseline, 6, 30 and 54 weeks	Mean age: 29 years 71% male Ethnicity NR	Mean duration of disease 2.63 PANSS total: NR	NR/NR/65 olanzapine = 21 risperidone = 21 haloperidol = 23
QUEST; Mullen, 2001	CGI (baseline, weekly, up to week 4and then monthly to 4 months), PANSS, HAM-D (baseline, 2 months, and 4 months)	Mean age=45.4 51.1% male 73.1% white 16.7% black 5.9% Hispanic 2.7% Asian 1.5% other	DSM-IV diagnosis Schizophrenia: 32.5% Schizoaffective disorder: 29.5% Bipolar I disorder: 13.3% Major depressive disorder: 10.4% Delusional disorder: 1.9% Alzheimer's dementia: 1.4% Schizophreniform disorder: 0.9% Other medical dementia: 0.7% Vascular dementia: 0.1% Substance abuse dementia: 0.1% Other: 7% Age at first diagnosis: 28.6 Psychiatric hospitalizations in last 4 months: 0.3 Duration of current symptoms: 163 wks Use of illicit drugs Past use: 32.2% Current use: 4.1% Current alcohol problem: 6.2% Previous alcohol problem: 30.4%	NR/NR/728

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Purdon, 2000 David, 1999 Jones, 1998 DB, RCT, multicenter (Canada)	37/NR/65 for symptoms, 55 for neurocognitive outcomes	Olanzapine/risperidone (p-value) Symptoms: Mean change PANSS total: NR Mean change PANSS positive:-2.14/-1.19 (0.72) Mean change PANSS negative: -2.76/-0.67 (0.72) Mean change PANSS gen psychopathology: -2.52/-1.33 (0.92) NR: QOL, resource utilization Cognitive outcomes: Cognitive Domains: olanzapine superior to risperidone on 2 of 6 domains: Motor skills: mean change o/r (p-value) 0.90/0.08 (p=0.04) Nonverbal fluency and construction: 0.81/-0.09 (p=0.006) Individual measures: olanzapine superior on 4 of 18 (grooved pegboard, verbal list learning, Hooper visual organization test, Rey-Taylor complex figure copy) General Cognitive Index: Comparison of change from baseline to wk 54: olanzapine superior to risperidone (data NR) p=0.004 Within group changes significant at: olanzapine: wk 6, 30 and 54 risperidone: wk 54
QUEST; Mullen, 2001	32.2% withdrawn/lost to fu NR/analyzed varied by outcome	Quetiapine, risperidone, p-value Withdrawal due to lack of efficacy: 57 (10.3%), 10 (5.8%) Mean changes: PANSS positive score: -3.2 vs -2.5, p=NS PANSS negative score: -3.1 vs -2.8, p=NS PANSS total score: -13 vs -11.8, p=NS HAM-D: -5.4 vs -4.0, p=0.028 CGI-I: quetiapine=risperidone (logistic regression model adjusting for differences in baseline EPS, diagnoses, age, and age at diagnosis p=0.087

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Purdon, 2000 David, 1999 Jones, 1998 DB, RCT, multicenter (Canada)	EPS: ESRS, Barnes Akathisia scale, Anti-EPS medications	ESRS: olanzapine/risperidone (p-value) Total score NR Parkinsonism: -1.43/+1.33 (p=0.14) Dystonia: -0.05/-0.14 (p=0.91) Dyskinesia: -0.57/+0.19 (p=0.12) Receiving EPS meds within 48hrs of last visit: olanzapine: 3/20 (15%), risperidone: 9/20 (45%)
QUEST; Mullen, 2001	EPS checklist that measured the severity of 22 EPS (including 15 motor system symptoms and 7 parkinsonian symptoms) using a 5-point scale (0=none, 1=a little, 2=moderate 3=quite a bit; 4=extreme) Safety was assessed through adverse event, defined as the development of any new medical condition or the deterioration of a preexisting medical condition after exposure to drug	Deaths: 0 vs 4 (2.3%) Any event 400 (72.3%), 107 (61.1%), NS Somnolence: 173 (31.3%), 27 (15.4%), p<0.05 Dry mouth: 80 (14.5%), 12 (6.9%), p<0.05 Dizziness: 70 (12.7%), 12 (6.9%), p<0.05 Insomnia: 65 (11.8%), 17 (9.7%), NS Headache: 52 (9.4%), 11 (6.3%), NS Agitation: 34 (6.1%), 3 (1.7%), p<0.05 Withdrawals due to Dry mouth: 2 (0.4%), 1 (0.6%) Dizziness: 6 (1.1%), 0 Weight gain: 14 (2.5%), 6 (3.4%), p-value nr Weight loss: 4 (0.7%), 0

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Purdon, 2000 David, 1999 Jones, 1998 DB, RCT, multicenter (Canada)	ESRS: olanzapine/risperidone (p-value) Total score NR Parkinsonism: -1.43/+1.33 (p=0.14) Dystonia: -0.05/-0.14 (p=0.91) Dyskinesia: -0.57/+0.19 (p=0.12) Receiving EPS meds within 48hrs of last visit: olanzapine: 3/20 (15%), risperidone: 9/20 (45%)	Overall 37 (57%) olanzapine: 43% risperidone: 67% haloperidol 61% Due to adverse events:12 (18%) olanzapine: 2 (9.5%) risperidone 3 (14%) haloperidol 7 (30%)	Analysis of effect of Anti-EPS meds on cognitive outcomes revealed one domain where significant effects were apparent at 6 and 54 weeks (immediate recall).
QUEST; Mullen, 2001	Quetiapine, risperidone Patients reporting EPS at LOCF: 38.6%, 39.2%, logistic regression model of the presence of any EPS in months 1-4 showed odds of a risperidone-treated patient having any EPS event were 1.33 times the odds of a quetiapine-treated patient having any EPS event, p=NS At least moderate EPS during trial: 161 (29.8%), 70 (40.9%); 1.94 times the odds for risperidone, p=0.003 Substantial EPS: 38 (7%), 35 (20.5%); 3.5 time the odds for risperidone, p<0.001 Anti-EPS medication use in patients with baseline EPS: 93/293 (31.7%), 47/91 (51.6%), p<0.001	Total withdrawals: 176 (31.8%), 59 (33.7%)Withdrawals due to AE: 48 (8.7%), 9 (5.1%)	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Reinstein, 1999 (QUEST subgroup)	Psychosis and: schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder (MDD), delusional disorder, Alzheimer's Disease, schizophreniform disorder, vascular dementia, or substance abuse dementia.	Quetiapine: flexible (mean 253.9 mg/d); oral Risperidone: flexible (mean 4.4 mg/d); oral Duration: 4 months	NR	NR
Ritchie, 2003 Pragmatic RCT, multicenter (Australia)	Patients > 60 with schizophrenia taking typical antipsychotics (depot or oral).	Starting dose: Olanzapine 5mg/d; 10mg after washout complete mean dose after switch: 9.9mg Risperidone 0.5mg/d, 1mg after washout complete mean dose after switch: 1.7mg Doses titrated by unblinded clinicians Duration: "Completion of switch"; stable dose of atypical and not on typical for 2 consecutive visits. Visit schedule = 14 days for those previously on oral neuroleptics, and "dose cycle: for depot drugs	4 weeks, while assigned drug titrated up. Depot drugs stopped on day 0, while assigned drug started	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Reinstein, 1999 (QUEST subgroup)	CGI PANSS DAI-10 HAM-D	NR	adult outpatients with psychotic disorders	NR/NR/751
Ritchie, 2003 Pragmatic RCT, multicenter (Australia)	BPRS, SANS, MADRS, MMSE, WHO-QOL(BREF) Assessed at baseline and each visit Initial switch phase followed by 6-month and 1-year (not complete at this publication) follow-up, but timing of assessments not clear	Mean age 70 19% male Ethnicity NR	Mean chlorpromazine equivalents Depot 326mg Oral 273mg 48.5% had TD at baseline Mean non-psychotropic drugs: 2.0/patient Mean major physical ailments: 1.2/patient Mean major surgical procedures (lifetime): 0.4	80/74/66 olanzapine: 34 risperidone: 32

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Reinstein, 1999 (QUEST subgroup)	NR	CGI; PANSS; DAI-10 Both groups had improvements in all efficacy measures (not significant). Higher percentage from quetiapine group had improvement in the CGI at each visit compared with risperidone group HAM-D: Quetiapine group had significantly greater improvement than risperidone group (p= 0.028)
Ritchie, 2003 Pragmatic RCT, multicenter (Australia)	14/0/61	Successful Switch: Crude OR 2.7(95% CI 0.7 to 10.2)* *Not based on an ITT population Recalculated crude RR based on ITT: O vs R 1.28 (95% CI 0.99 1.74) Mean time to complete switch: olanzapine 40.6 days risperidone 40.4 days Symptoms: NS difference between groups on change in BPRS, SANS, MADRS SS improvement within groups on BPRS, SANS, MADRS QOL: Olanzapine: within group SS change on physical, psychological well-being and health satisfaction Risperidone: within group changes NS O vs R: SS difference on change in psychological well-being score (p=0.002) (ANCOVA analysis)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Reinstein, 1999 (QUEST subgroup)	EPS checklist Anti-EPS medication Adjusted study medication dose	NR
Ritchie, 2003 Pragmatic RCT, multicenter (Australia)	EPS: SAS, AIMS, BARS Other: "standard reporting of adverse events, weight changes, and a study-specific pro forms was used for assessing side effects associated with elevated prolactin and cholinergic antagonism"	SAS and BARS: SS change from baseline (reduction) in both groups NS difference between groups AIMS: SS change from baseline in olanzapine group, not in risperidone group; NS difference between groups Other: Sedation and hypotension/dizziness > olanzapine (NS) GI symptoms > risperidone (NS) Changes in libido (increases) > olanzapine (NS) Weight gain: SS within groups mean increase: olanzapine 2.8kg, risperidone 2.1kg (NS)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Reinstein, 1999 (QUEST subgroup)	EPS checklist: extrapyramidal events in both groups declined over treatment period, with no significant differences between groups in overall occurrence; risperidone group more likely to have extrapyramidal event and more likely ($p < 0.001$) to be one requiring adjustment of study medication or adjunctive medication than quetiapine group	NR / NR	
Ritchie, 2003 Pragmatic RCT, multicenter (Australia)	SAS and BARS: SS change from baseline (reduction) in both groups NS difference between groups AIMS: SS change from baseline in olanzapine group, not in risperidone group; NS difference between groups	14 (21%) total withdrawals 3 (in risperidone arm = 9%) due to AEs	Not ITT. Only switch data presented, 6-month and 1 year follow-up data to come.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Ritchie, 2006 Open-label x 6 months, multicenter (Australia)	> 60 years of age, previously treated with a typical antipsychotic drug for schizophrenia, imperfect symptom control or troublesome side effects on the typical drug and have had to complete cross-over Richie, 2003 study.	O: (n = 34), [30 pts had successfully switched from a typical antipsychotic] R: (n = 32) [22 had successfully switched from a typical antipsychotic]	NA	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.
Sacchetti 2009 DB RCT 23 Italian departments of mental health. The MOZART Study	Inclusion: DSM-IV diagnosis of schizophrenia, a history of resistance and/or intolerance to at least three acute cycles with different antipsychotics given at therapeutic doses, PANSS score ≥80, and CGI-S score ≥4 Exclusion: current DSM-IV Axis I comorbid disorders; concomitant acute or unstable physical illnesses; clinically significant abnormal laboratory test values; a positive urine screen for substances of abuse; any contraindication to ziprasidone or clozapine; and treatment with the investigational drugs during the previous 3 months; female patients of childbearing potential not using contraception	Ziprasidone (80–160 mg/day, n=73) vs. or clozapine (250–600 mg/day, n=74) Duration 18 weeks	1- to 7-day screening period and a 3-day placebo run-in period	Benzodiazepines and anticholinergic agents
Sacchetti, 2008 The QUERISOLA trial DB RCT Italy	18 and 65 years; diagnosis of schizophrenia ; a total score of ≥ 70 on the Positive and Negative Syndrome Scale (PANSS) ; and no exposure to depot antipsychotics in the previous 6 weeks.	Risperidone 590.0 ± 175 mg n=25 Olanzapine 5.1 ± 1.5 mg n=25 Quetiapine 15.1 ± 5.8 n=25 8 weeks	NR	YES - zolpidem or flurazepam for insomnia , or anticholinergics or benzodiazepines for movement disorders

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Ritchie, 2006 Open-label x 6 months, multicenter (Australia)	q 6 weeks BPRS, SANS, MADRS, MMSE	Mean age: O: 69.7 ± 7.3 R: 69.4 ± 5.0 p=0.973 Gender (%) male: O: 10 (29.4%) R: 8 (29.6%) % unmarried: O 28 (82.4%) R: 20 (74.1%)	"No clinical or demographic differences between the groups"	NA/NA/61
Sacchetti 2009 DB RCT 23 Italian departments of mental health. The MOZART Study	Change from baseline in PANSS total; endpoint change from baseline in PANSS positive, negative and general psychopathology subscales, CGI-S, CGI-I, CDSS, GAF, and DAI-10 as well as response rates based on ≥20%, ≥30% and ≥40% improvements in PANSS total scores. Assessments occurred at baseline and then weekly.	Mean age 40 yrs 69% male Ethnicity NR	Resistance only 40% Intolerance only 16% Both resistance and intolerance 44%	162/157/147
Sacchetti, 2008 The QUERISOLA trial DB RCT Italy	PANSS, Simpson–Angus Scale for extrapyramidal symptoms (SAS), Barnes Akathisia Rating Scale (BARS) , and Abnormal Involuntary Movement Scale (AIMS) scores, and vital signs and body weight were all assessed at the screening visit and 7, 14, 21, 28, 35, 42, and 56 days	Mean age 39.94 56% male Ethnicity NR	PANSS Total Risperidone 96.0±20.5 Olanzapine 98.5±20.0 Quetiapine 101.3±20.0	NR/NR/75

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Ritchie, 2006 Open-label x 6 months, multicenter (Australia)	8/0/61	BPRS Overall, between BL and 6 month follow-up: O: p=0.001; R: p= 0.044 Between end of crossover and 6-month follow-up: O: p=0.329; R: p=0.511 Group differences at 6-month follow-up (ANCOVA); p=0.303 SANS Between BL and 6 month follow-up: O: p= 0.002; R: p= 0.030 Between end of crossover and 6 month follow-up: O: p=0.159; R: p=0.194 Group differences at 6 month follow-up (ANCOVA): p= 0.212 MADRS Between BL and 6 month follow-up: O: p=0.008; R: 0.p=114 Between end of crossover and 6 month follow-up: O: p=0.549; R: p=0.156 Group differences at 6 month follow-up (ANCOVA): p=0.402 WHO-QOL: O: (n=29); R (n=21) (adjusted mean group differences on 6 month domains after co-varying for BL QOL. All effects favored Olanzapine Physical: p=0.034; Psychological: p=0.100 (NS) Social: p=0.015 Environmental: p=0.643 (NS) Overall QOL: p=0.040 Health Satisfaction p=0.031
Sacchetti 2009 DB RCT 23 Italian departments of mental health. The MOZART Study	56/NR/146	Ziprasidone (n=71) vs. Clozapine (n=73) Mean (±SD) change (LOCF) PANSS total score −25.0±22.0 vs. −24.2±22.5 PANSS-P −6.0±7.8, vs. −7.0±7.2 PANSS-N −7.6±6.7 vs. −6.1±6.5 PANSS general psychopathology subscale score −11.3±11.4 vs. −11.4±12.8 CGI-S score −0.6±0.9 vs. −0.6±0.9 CGI-I score endpoint 3.2±1.5 vs. 3.3±1.3
Sacchetti, 2008 The QUERISOLA trial DB RCT Italy	14/2/61 PP	Quetiapine vs. risperidone vs. olanzapine mean reductions PANSS total scores 37.0 vs. 32.1 vs. 34.4 ≥ 40% reduction from baseline in PANSS total score at Week 8 10/21 [48%] vs. 8/20 [40%] vs. 8/20 [40%]).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Ritchie, 2006 Open-label x 6 months, multicenter (Australia)	AIMS, BARS, SAS, WHO-QOL (BREF) Other: Safety was assessed by "standard reporting of adverse events, weight changes, and a study-specific pro-forma was used for assessing side effects associated with elevated prolactin and cholinergic antagonism". Non-compliant: counting returned tables.	Weight gain between BL and 6 month: O (n=34) gained an average of 4.3 kg (SD =4.6, median=3.0kg) vs. R: (n=27) average gain 1.7kg (SD=4.7; median 1.0kg) (difference p=NS) Between BL and 6 month: O 24/34 (70.6%) gained mean increase 7.3 kg; median 6.0kg vs. R 14/27 (51.9%) gained mean increase =4.6kg; median =4.0 kg) (difference p=NS) MMSE scores stable (between BL and 6 month follow-up) (mean difference, p=NS) AE occurring > 5%: O vs. R Gastrointestinal: 14 vs. 7 CNS: 9 vs. 4 Musculoskeletal 6 vs. 3 Psychiatric: 7 vs. 5 -- not captured specifically in study rating scales. Infection 8 vs. 6 CVS: 7 vs. 10 Renal: 0 vs. 5 Dermatological: 3 vs. 3 Endocrine: 6 vs. 0 Total AE: 61 vs. 36--"no significant differences observed between the two groups"
Sacchetti 2009 DB RCT 23 Italian departments of mental health. The MOZART Study	Severity, duration, and possible relation to study drug of all observed or volunteered adverse events (AEs) were recorded. Simpson–Angus Scale , the Barnes Akathisia Scale and Abnormal Involuntary Movement Scale; laboratory tests; hematologic monitoring; vital signs and ECG	Ziprasidone(n=73) vs. Clozapine(n=73) Increased salivation 0% vs. 28.8% Tachycardia 2.7% vs. 28.8% Dizziness 4.1% vs. 9.6% Headache 6.8% vs. 4.1% Nausea 6.8% vs. 8.2% Somnolence 4.1% vs. 23.3% Insomnia 9.6% vs. 2.7% Any adverse event 71.2% vs. 79.5%
Sacchetti, 2008 The QUERISOLA trial DB RCT Italy	Spontaneously reported emergent moderate-to-severe AEs; any clinically relevant abnormalities in the physical examination, vital signs, blood chemistry, and hematology; and changes from baseline in body weight and SAS, BARS, and AIMS scores.	Five patients (6.7%) spontaneously reported an AE of moderate intensity during the trial: quetiapine group, no events; risperidone group, one event (parkinsonian symptoms); olanzapine group, four events (weight gain, anxiety, pneumonia, scrotal eczema). ≥ 7% increase in baseline body weight occurred in quetiapine 8%, risperidone 8%, olanzapine 29%

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Ritchie, 2006 Open-label x 6 months, multicenter (Australia)	AIMS At 6-month after adjusting for BL: NS Overall, between BL and 6 month follow-up: O: (p=0.054); R (p=0.964) Between end of crossover and 6-month follow-up: O: (p=0.622); R: (p=0.055), Group differences at 6-month follow-up (ANCOVA); p=0.190 SAS: Between BL and 6-month followup: O: p=0.001; R: p<0.001 Between end of crossover and 6 month follow-up: O: p=0.273; R: p=0.249 Between-group differences at 6 months after controlling for BL scores; p=0.647 Akathisia: 6 month: (R: n=9, 33.3%; O n=10, 29.4%)-experienced some degree of post-baseline akathisia (mostly mild/moderate in degree). Of the 19, 9 (O=6, 17.6%; R n=3, 11.1%) were new cases who had not experienced akathisia at baseline. NS	26 (O: 9 (26.5%); R 15 (46.9%) p=0.09 (NS)/6 (2 in the o arm and 4 in the R arm. In the O group, there were 61 Total AE (1.79 per patient) vs. 36 in the R group (1.33 per patient)	Unable to recruit target population of 80 patients...post-hoc power calculation --sample size was sufficient for analysis.
Sacchetti 2009 DB RCT 23 Italian departments of mental health. The MOZART Study	Ziprasidone vs. Clozapine Change score, mean [95% CI] Simpson–Angus Scale −0.21 [−0.30 to −0.12] vs. −0.06 [−0.14 to 0.02] Barnes Akathisia Scale −0.37 [−0.64 to −0.11] vs. −0.22 [−0.44 to 0.01]∗ Abnormal Involuntary Movement Scale −0.15 [−0.08 to −0.22] vs. −0.08 [−0.18 to 0.03]	56 withdrawals 31 due to AEs	
Sacchetti, 2008 The QUERISOLA trial DB RCT Italy	SAS scores (lower quartile, median, upper quartile) Week 8 Risperidone 1.00, 3.00, 10.25 Olanzapine 0.00, 0.50, 4.25 Quetiapine 0.0, 0.0, 1.0 Risperidone vs quetiapine P = 0.005, other comparisons NS	14 withdrawals 1 due to AEs	Completers analysis, ITT reported in graphs.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Sajatovic, 2002 (QUEST sub-group analysis, Mullen, 2001) RCT, open-label, multicenter	Psychosis and: schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder (MDD), delusional disorder, Alzheimer's Disease, schizophreniform disorder, vascular dementia, or substance abuse dementia. No significant medical disorders, no current clozapine treatment or history of non-response to clozapine, and no history of drug-induced agranulocytosis. For this analysis, Mood Disorder was classified as: 1) schizoaffective disorder, 2) bipolar disorder, and 3) MDD	quetiapine 50-800mg/d risperidone 1-6 mg/d Duration: 4 months	none	Any deemed medically necessary. Additional antipsychotics allowed only after attempt to stabilize on assigned drug for 1 month. No depot drugs, clozapine or olanzapine allowed. Mood stabilizers and antidepressants could be continued if dose stable x 2 wks. Rescue meds allowed.
Schering-Plough, Data on file. Study 041022 DB RCT Multicenter (USA, Ukraine, Russia)	Inclusion: 18 years of age or older with a DSM-IV text-revised diagnosis of schizophrenia (of the paranoid, disorganized, catatonic, or undifferentiated subtypes) with an acute exacerbation of psychotic symptoms; positive response to previous antipsychotic medication other than clozapine; PANSS total score >60 and a score of >4 on at least 2 of 5 PANSS positive subscale items (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution); CGI-S score >4 at baseline Exclusion: clinically significant medical conditions or abnormal laboratory or physical examination findings; diagnosis of residual type schizophrenia, schizoaffective disorder, or coexisting psychiatric disorder coded on Axis I; substance abuse; a >20% decline in PANSS total score from screening to baseline; those at risk of harming themselves or others	Asenapine (5mg or 10mg bid) sublingual Placebo bid Olanzapine (10mg to 20mg qd) oral 6 weeks	2-day taper period	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Sajatovic, 2002 (QUEST sub-group analysis, Mullen, 2001) RCT, open-label, multicenter	PANSS CGI HAM-D	Mean age 45 73 % white 51% male	33.7% taking mood stabilizers 33.7 taking antidepressants 57% of total population classified as "mood disorder"	NR/NR/729 Of these, 419 with mood disorders
Schering-Plough, Data on file. Study 041022 DB RCT Multicenter (USA, Ukraine, Russia)	change from baseline to endpoint (day 42) in the PANSS total score; change from baseline to endpoint in PANSS subscale scores for positive, negative, and general psychopathology, the PANSS Marder factor score, PANSS responders, CGI-S, CGI-I scores, Calgary Depression Scale for Schizophrenia (CDSS), Modified International Suicide Prevention Trial, Scale for Suicidal Thinking (ISST-Modified), and Readiness to Discharge Questionnaire (RDQ).	Asenapine vs Placebo vs Olanzapine Mean age (SD): 44 (9.03) vs 41.9 (9) vs 41.6 (10.41) Male: 74.4% vs 79.6% vs 78.3% Caucasian: 50% vs 45.2% vs 44.6% Black: 42.2% vs 46.2% vs 46.7% Asian: 2.2% vs 0 vs 2.2% Other: 5.6% vs 8.6% vs 6.5%	Asenapine vs Placebo vs Olanzapine Current Principal Psychiatric Diagnosis Schizophrenia ---Catatonic subtype: 0 vs 0 vs 0 ---Disorganized subtype: 3.3% vs 3.2% vs 3.3% ---Of the paranoid subtype: 93.3% vs 90.3% vs 89.1% ---Undifferentiated subtype: 3.3% vs 6.5% vs 7.6%	NR/NR/277

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Sajatovic, 2002 (QUEST sub-group analysis, Mullen, 2001) RCT, open-label, multicenter	NR/NR/419	Psychosis Efficacy: NS difference on PANSS or CGI, reported in Muller 2001 Depression: HAM-D Scores Change from baseline to LOCF: quetiapine ~5.6, risperidone ~4 (p=0.028) % Change from baseline: quetiapine, risperidone, p-value All patients: -44.6%, -34.4, p=0.0015 Mood disorders: -44.1, -35.7, p=0.0364 NS by individual diagnosis Non-mood disorders: -45.6, -31.1, p=0.0083 HAM-D score >/=20 Mood disorders: -47%, -34%, p=0.0051 Non-mood disorders: Q>R, p=0.008 HAM-D score 10-19, or <10 NS difference for either group.
Schering-Plough, Data on file. Study 041022 DB RCT Multicenter (USA, Ukraine, Russia)	142/21/259	"The study did not meet its primary endpoint, there was no significant difference between asenapine and placebo or olanzapine and placebo in the LS mean changes in the PANSS total score from baseline to endpoint or at any trial visit" "No statistically significant differences were observed between asenapine and placebo or between olanzapine and placebo in the LS mean change from baseline to endpoint in any secondary efficacy measure defined for this trial"

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Sajatovic, 2002 (QUEST sub-group analysis, Mullen, 2001) RCT, open-label, multicenter	Substantial EPS defined as 1) use of Anti-EPS med, 2) decrease in dosage, or 3) discontinuation. Assessed by symptom checklist provided by AstraZeneca (not provided)	Patients with Mood disorders: risperidone > quetiapine (p<0.001, numbers not reported) Patients without Mood disorders: NS difference (p=0.063)
Schering-Plough, Data on file. Study 041022 DB RCT Multicenter (USA, Ukraine, Russia)	NR	Asenapine vs Placebo vs Olanzapine n (%) All AEs: 62 (68.9) vs 56 (60.2) vs 58 (63.0) All serious AEs: 6 (6.7) vs 3 (3.2) vs 8 (8.7) Headache: 18 (20.0) vs 15 (16.1) vs 11 (12.0) Anxiety: 10 (11.1) vs 7 (7.5) vs 9 (9.8) Insomnia: 10 (11.1) vs 11 (11.8) vs 8 (8.7) Agitation: 6 (6.7) vs 6 (6.5) vs 6 (6.5) Nausea: 6 (6.7) vs 11 (11.8) vs 5 (5.4) Constipation: 5 (5.6) vs 7 (7.5) vs 8 (8.7) Dyspepsia: 5 (5.6) vs 4 (4.3) vs 10 (10.9) Sedation: 5 (5.6) vs 4 (4.3) vs 12 (13.0) Weight Increased: 5 (5.6) vs 1 (1.1) vs 8 (8.7)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Sajatovic, 2002 (QUEST sub-group analysis, Mullen, 2001) RCT, open-label, multicenter	NR	NR / NR	Analysis of effect of EPS on HAM-D scores by ANCOVA: subset of patients who had at worst mild akinesia, hypokinesia or akathisia at baseline and did not get worse during trial showed quetiapine superior to risperidone on HAM-D score (p=0.017) - not clear which group of patients, size of group, or timing of assessments.
Schering-Plough, Data on file. Study 041022 DB RCT Multicenter (USA, Ukraine, Russia)	NR	Asenapine vs Placebo vs Olanzapine Total withdrawals: 48 vs 45 vs 49 Withdrawals due to AEs: 6 vs 5 vs 11	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Schering-Plough; Data on File. Study 041021 DB RCT Multicenter (USA, Ukraine, Russia)	Inclusion: 18 years of age or older with a text-revision DSM-IV diagnosis of schizophrenia (of the paranoid, disorganized, catatonic, or undifferentiated subtypes) with an acute exacerbation of psychotic symptoms; positive response to previous antipsychotic medication other than clozapine; PANSS total score ≥60 and a score of ≥4 on at least 2 of 5 PANSS positive subscale items (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution); CGI-S score ≥4 at baseline Exclusion: clinically significant medical conditions or abnormal laboratory or physical examination findings; diagnosis of residual type schizophrenia, schizoaffective disorder, or coexisting psychiatric disorder coded on Axis I; substance abuse; a ≥20% decline in PANSS total score from screening to baseline; those at risk of harming themselves or others	Asenapine 5mg BID vs Asenapine 10 mg BID vs Placebo BID vs Olanzapine 15 mg BID 6 weeks	NR	NR
Schering-Plough 25517 DB RCT Multicenter: Russia, Australia, South Africa, 8 countries in Europe	Inclusion: Aged 18 or older with a DSM-IV TR diagnosis of schizophrenia or schizoaffective disorder; PANSS total score>=6 and a score of >=4 on at least 2 of 5 PANSS positive subscale items; CGI-S score >=4 at baseline; and have never received neuroleptic treatment before or shown a response with a neuroleptic other than clozapine. Exclusions: significant medical conditions or abnormal lab or physical exam diagnosis of residual type schizophrenia or coexisting Axis I substance abuse disorder; risk of harming self or others	Sublingual Asenapine 5 or 10 mg BID, flexible dose, 52 weeks. Oral olanzapine 10 to 20 mg QD, flexible dose, 52 weeks. Double-dummy design (active vs placebo). Patients were hospitalized for a minimum of 2 weeks and then monitored on outpatient basis.	3 to 9-day run-in period	NR
Schering-Plough 25543 DB RCT Multicenter: Australia, Romania, South Africa, 13 countries in Europe	Inclusion: Aged 18+ with DSM-IV TR diagnosis of schizophrenia of paranoid, disorganized, catatonic, residual, or undifferentiated subtype; PANSS negative subscale >=20 at screening and baseline with a score >=4 (moderate) on at least 3 of the Marder factors for negative symptoms; PANSS positive subscale score less than the PANSS negative subscale score at screening and at baseline; and stable disease in the last 5 months. Exclusions: significant medical conditions or abnormal lab or physical exam; coexisting Axis I primary diagnosis including depression or substance abuse; risk of harming self or others	Asenapine 5 or 10 mg BID, flexible dose, 26 weeks. Olanzapine 5 to 20 mg QD, flexible dose, 26 weeks. Double-dummy design (active vs placebo). 30-day stable observation period followed by baseline visit. Active treatment period: 4 week AP switch period followed by 22-week monotherapy.	4-week AP switch period preceding monotherapy	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Schering-Plough; Data on File. Study 041021 DB RCT Multicenter (USA, Ukraine, Russia)	PANSS total score; PANSS subscale scores for positive, negative, and general psychopathology; the PANSS Marder factor score, CGI-S, CGI-I scores, CDSS, Fleming/Potkin Battery, cognitive function scale, HAS, RDQ, ISST-Modified, quality of life scales and PETiT.	Mean age: 40.2 years Male: 70.3% Caucasian: 46.3% Black: 44.9% Asian: 1.7% Other: 7.1%	Diagnosed with schizophrenia (paranoid subtype): 88.5%	NR/NR/417
Schering-Plough 25517 DB RCT Multicenter: Russia, Australia, South Africa, 8 countries in Europe	PANSS, CGI-S, CGI-I, SWN, physical and mental component scales of the SF-12 at baseline and endpoint. Follow-up up to 30 days after the last dose.	Mean age 36.6 54% male 92.6% Caucasian 5.7% Black 0.9% Asian	77.8% Schizophrenia, paranoid subtype 13.1% Schizoaffective disorder Mean CGI-S at baseline 4.8	Screened NR Eligible NR 1215 randomized
Schering-Plough 25543 DB RCT Multicenter: Australia, Romania, South Africa, 13 countries in Europe	Change from baseline at 52 weeks in NSA total score, QLS, PANSS subscale scores, PANSS Marder factor scores, CDSS, CGI-I, CGI-S, CNS Vital Signs Neurocognitive Test Battery, PETiT, level of function scale, and Q-LES-Q (leisure time activities and social relations) scales. Follow-up up to 30 days after end of treatment visit	Mean age 40.5 68.2% male 89.4% Caucasian 6.9% Black 0.2% Asian	62.6% paranoid subtype	Screened NR Eligible NR 481 enrolled

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Schering-Plough; Data on File. Study 041021 DB RCT Multicenter (USA, Ukraine, Russia)	189/20/386	Asenapine 5mg BID vs Asenapine 10 mg BID vs Placebo BID vs Olanzapine 15 mg BID; *P* values are versus placebo Mean change in PANSS total score: -14.5 (*P*=0.2556) vs -13.4 (*P*=0.3046) vs -11.1 vs -16.5 (*P*=0.0168) Mean change in PANSS positive subscale score: -5.5 (*P*=0.0119) vs NR (*P*=NS) vs -3.6 vs -5.6 (*P*=0.0132) Asenapine 10 BID resulted in a statistically significantly greater LS mean increase from baseline to endpoint in the Q-LES-Q leisure time activities and social relations subscale scores. A statistically significant difference between olanzapine and placebo on the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) leisure time activities subscale at endpoint. No statistically significant difference between any active treatment and placebo in the CGI-I, CDSS, Fleming/Potkin Battery, cognitive function HAS, ISST-Modified, quality of life scale or PETiT scales.
Schering-Plough 25517 DB RCT Multicenter: Russia, Australia, South Africa, 8 countries in Europe	691 (56.8%) withdrew 26 (2.1%) loss to follow-up 1166 (93%) analyzed	Asenapine vs Olanzapine: Mean change from baseline to endpoint: PANSS total score: -21.0 vs -27.5 (p<0.0001 in favor of olanzapine) CGI-S: -1.2 vs -1.6 Mean CGI-I score at endpoint: 2.9 v. 2.4 CGI-I score <3 (much or very much improved): 52% vs 66% CGI-I score >=3 (minimal improvement): 48% vs 34% No differences between groups on SWN or SF-12, or in living situations, employment, or level of functioning.
Schering-Plough 25543 DB RCT Multicenter: Australia, Romania, South Africa, 13 countries in Europe	132 (27.4%) withdrew 5 (1%) lost to followup 433 (90%) analyzed	Asenapine vs olanzapine: Mean change from baseline to day 182 in NSA: -12.5 vs -12.5. Change in CDSS: -0.8 vs -0.2; P=0.0055. No differences between treatments in NSA global scores, QLS total score, PANSS total score, CGI-S score, CGI-I response rates, and Q-LES-Q social relations or leisure time activities scores.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Schering-Plough; Data on File. Study 041021 DB RCT Multicenter (USA, Ukraine, Russia)	Adverse events, extrapyramidal symptoms, metat	Asenapine 5mg BID vs Asenapine 10 mg BID vs Placebo BID vs Olanzapine 15 mg BID Dizziness: 8.7% vs 4.9%vs 2.0% vs 7.8% Hypoesthesia oral: 2.9% vs 3.9% vs 0.0% vs 0.0% weight increased: 3.8%vs 2.9% vs 0.0% vs 4.9% Hyperprolactinemia (>4 times the upper limit of normal): 6.0% vs 3.1% vs 2.1% vs 0.0% Fasting glucose values (>1.5 times the upper limit of normal): 3.7% vs 0.0% vs 1.3% vs 5.1% Triglyceride levels (>5.65 mmol/L): 0.0% vs 1.3% vs 3.9% 5.1% Weight gain (>7%): 4.8% vs 5.9% vs 1.0% vs 16.7%
Schering-Plough 25517 DB RCT Multicenter: Russia, Australia, South Africa, 8 countries in Europe	EPS: SAS, BARS, and AIMS scales Metabolic/laboratory parameters Weight change from baseline to endpoint	Asenapine vs olanzapine: Suicide attempts: 1.2 vs 1.9% Completed suicide: n=5 (<1%) vs n=1 (<1%) Weight increase: 12 vs 29% Mean (SD) change in weight: 0.9 (4.8) kg vs 4.2 (7.6) kg Schizophrenia/psychosis: 8 vs 5% Insomnia: 7 vs 5% Sedation: 8 vs 10% Somnolence: 9 vs 10% Gastrointestinal symptoms: 9 vs 7% Akathisia: 8 vs 4% Prolactin levels decreased in both treatment groups.
Schering-Plough 25543 DB RCT Multicenter: Australia, Romania, South Africa, 13 countries in Europe	EPS Metabolic/laboratory parameters Weight change from baseline to endpoint	Asenapine vs olanzapine, % of group: Gained >=7% of body weight: 7.9 vs 24.6 Abnormal increase in prolactin: 7 vs 3.5 Insomnia: 15.8 vs 10.8 Headache: 12.9 vs 9,.6 Somnolence: 12.4 vs 11.3 Anxiety: 9.5 vs 8.3 Schizophrenia: 7.1 vs 3.8 Agitation: 6.2 vs 1.3 Nausea: 5.4 vs 3.8 Fatigue: 4.6 vs 6.7 Weight increased: 4.6 vs 21.3

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Schering-Plough; Data on File. Study 041021 DB RCT Multicenter (USA, Ukraine, Russia)	Asenapine 5mg BID vs Asenapine 10 mg BID vs Placebo BID vs Olanzapine 15 mg BID Treatment-emergent extrapyramidal symptoms: 6.7% vs 11.8% vs 7.0% vs 6.9%	Total withdrawals: 189 Withdrawals due to AEs: 39	
Schering-Plough 25517 DB RCT Multicenter: Russia, Australia, South Africa, 8 countries in Europe	Asenapine vs olanzapine EPS: 18% vs 8%, most commonly akathisia: 8% vs 4% Mean (SD) change from baseline to endpoint in EPS scales: SAS: -0.4 (2.5) vs -0.7 (2.7) BARS: -0.1 (1.9) vs -0.3 (1.5) AIMS 7 total score: -0.1 (1.3) vs -0.2 (1.2)	total N; % of asenapine vs olanzapine: 691 withdrew; 61.5% vs 42.8% 193 due to AE; 17.1% vs 12.2%	
Schering-Plough 25543 DB RCT Multicenter: Australia, Romania, South Africa, 13 countries in Europe	Asenapine vs olanzapine: EPS: 8.3% vs 3.3% Akathisia: 2.9 vs 1.3% Parkinsonism 2.1 vs 1.7%	total N; % of asenapine vs olanzapine 132 withdrew; 35.3% vs 19.6% 54 due to AE; 14.9% vs 7.5%	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Schering-Plough, Data on file. Study 7501012 DB RCT	Inclusion: 18 years of age or older with a DSM-IV text-revised diagnosis of schizophrenia; receiving continuous antipsychotic treatment for at least 1 year; stable at time of entry with a history of >1 episode of acute schizophrenia in the 3 years preceding screening Exclusion: a concurrent Axis 1 diagnosis other than schizophrenia at screening; a PANSS score >80 or a CGI-S score >4 at screening; mental retardation or organic brain syndrome; a substance-induced psychotic disorder	All patients received 5 mg or 10 mg flexible dose asenapine during 4 weeks open label phase 1 and 22 weeks open-label phase 2 Patients were then randomized 1:1 to 26 weeks DB treatment with arsenapine (5 or 10mg) BID or placebo Treatments administered sublingually	Cross titration from prior medication to asenapein 5 or 10 mg BID in phase 1.	NR
Sethuraman, 2005 Sub-analysis of Tran 1997	Same as Tran 1997.	Same as Tran 1997	Same as Tran 1997	Same as Tran 1997
Simpson, 2004 DB, multicenter, parallel, flexible-dose Inpatients	Between Ages 18-55 yrs, females not of childbearing potential, hospitalized no more than 2 consecutive weeks immediately before screening, schizophrenia/schizoaffective disorder, persistent psychotic symptoms for the week before hospitalization, score of >4 before screening on CGI, score of >4 on at least one of the Positive and Negative Syndrome Scale, normal laboratory results, normal ECG results, negative results on urine drug screen a entry.	Olanzapine (n= 133): daily mean dose- 11.3 mg Ziprasidone (n= 136): daily mean dose- 129.9 mg 6 weeks duration	NR	Lorazepam, benztropine.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Schering-Plough, Data on file. Study 7501012 DB RCT	Time to relapse or impeding relapse as per criteria defined a priori; time to early discontinuation, change from baseline of the double-blind treatment period in the PANSS total score, PANSS Marder factor scores, CGI-S, CGI-I, CDSS, ISST Modified; cognitive function	Asenapine vs Placebo Mean age (SD): 89 (45.9) vs 76 (39.6) years Male: 54.1% vs 60.4% Caucasian: 72.7% vs 72.9% Black: 11.3% vs 9.4% Asian: 15.5% vs 17.2% Other: 0.5% vs 0.5%	Asenapine vs Placbo DSM-IV Diagnosis, n (%) Schizophrenia, catatonic subtype: 1% vs 0.5% Schizophrenia, disorganized subtype: 0 vs 0.5% Schizophrenia, of the paranoid subtype: 82% vs 81.3% Schizophrenia, undifferentiated subtype: 13.4% vs 13.5% Schizophrenia, residual type: 3.6% vs 4.2% Schizoaffective disorder: 0 vs 0	NR/NR/NR
Sethuraman, 2005 Sub-analysis of Tran 1997	Proportion of time spent in remission Remission definitions: 1. Scores ≤ 3 concurrently on PANSS items: delusions, conceptual disorganization, hallucinatory behavior, blunted affect, passive/apathetic social withdrawal, lack of spontaneity and conversation flow, mannerisms and posturing, unusual thought content 2. 50% reduction in BPRS Total score, scores of ≤ 3 concurrently on each of the BPRS psychosis items and CGI-S score ≤ 3	Same as Tran 1997	Same as Tran 1997	Same as Tran 1997
Simpson, 2004 DB, multicenter, parallel, flexible-dose Inpatients	Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression (CGI), CGI improvement scale, Positive and negative Syndrome Scale, Calgary Depression Scale for Schizophrenia, fasting lipid profiles, fasting glucose, insulin measurements, electrocardiography, monitoring of vital signs and body weight	Mean age: 37.7 years Male: 176/269(65%) Female: 93/269(35%) White: 141/269(52%) Black: 65/269(24%) Asian: 6/269(2%) Hispanic: 28/269(10%) Other: 7/269(3%)	In-Patient population: 100%	367/269/269

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Schering-Plough, Data on file. Study 7501012 DB RCT	179/6/ITT 382	Time to relapse was longer in the asenapine group compared with the placebo group (*P*<0.0001; RR, 0.26) Time to termination was significantly longer in the asenapine group compared with the placebo group throughout the double-blind treatment period (*P*<0.0001; RR, 0.47) Statistically significant difference in favor of asenapine in the change from baseline of the double-blind period to endpoint of the double-blind period for PANSS total score, PANSS Marder Factor scores, and CGI-S.
Sethuraman, 2005 Sub-analysis of Tran 1997	Same as Tran 1997	Proportion of time spent in remission for olanzapine vs risperidone: Definition 1: 40% vs 31%, p=0.03 Definition 2: 18% vs 11%, p=0.01
Simpson, 2004 DB, multicenter, parallel, flexible-dose Inpatients	115 (42.6%)/NR/269	BPRS Total Scores: Difference at endpoint: p=0.77, CI=-2.36 to 3.18 CGI Severity Scale: p=0.95, CI -0.27 to 0.29 Positive and Negative Syndrome Scales: CI= -4.44 to 5.21 CGI Improvement Scale: Very much improved: Z: 15.1% vs O: 17.8% Much improved: Z: 34.1% vs O: 38.8% Calgary Depression Scale for Schizophrenia: p=0.38, 95% CI= -0.48 to 1.24 Serum lipid profile results- Median changes: Total cholesterol: O: +19.5 mg/dl vs Z: -1 mg/dl; p<0.0001 Triglycerides: O: +26 mg/dl vs Z: -2 mg/dl; p=0.77 LDL cholesterol: O: +13 mg/dl vs Z: -1 mg/dl; p=0.78 Homocystine levels: O: -1.06 mg/dl vs Z: -0.38 mg/dl; p<0.005 Apolipoprotein B levels: O: +9.0 mg/dl vs Z: -3.0 mg/dl; p<0.0001 Glucose metabolism results- Median changes: Fasting serum glucose levels: Z: 1.0 mg/dl vs O: 1.0 mg/dl Fasting serum insulin levels: O: +3.30 vs Z: +0.25; p=0.051 C-peptide levels: O: +0.46 vs Z: +0.16; p=0.07 Uric acid levels-Median changes: O: + 0.65 vs Z: +0.10; p<0.004

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Schering-Plough, Data on file. Study 7501012 DB RCT	Adverse events; Effect on Weight; Metabolic/Laboratory Parameters	Asenapine vs Placebo At least one treatment-related adverse event: 22.7% (44/194) vs 27.1% (52/192) Anxiety: 8.2% vs. 10.9% Weight increased: 6.7% vs. 3.6% Insomnia: 6.2% vs. 13.5% Mean (SD) change in weight: 0.0 (3.41) vs -1.2 (3.96) kg >7% gain from baseline: 4% vs 1% Markedly abnormal biochemistry values in creatinine kinase: 1.7% vs 1 0.6% Markedly abnormal biochemistry values in creatinine: 1.1% vs 0% Markedly abnormal biochemistry values in AST: 2.8% vs 0.6% Markedly abnormal biochemistry values in ALT: 1.7% vs 0.6% Markedly abnormal metabolic chemistry values in LDL: 0.6% vs 0% Markedly abnormal metabolic chemistry values in triglycerides: 1.5% vs 0.8% Markedly abnormal metabolic chemistry values in high glucose: 5.4% vs 3.3% Markedly abnormal metabolic chemistry values in HbA1c: 2.3% vs 0.6%
Sethuraman, 2005 Sub-analysis of Tran 1997	NR	NR
Simpson, 2004 DB, multicenter, parallel, flexible-dose Inpatients	Patient report, physical examinations	Body as a whole: Z: 52(38.2%) vs O: 39(29.3%) Cardiovascular: Z: 7(5.1%) vs O: 10(7.5%) Digestive: Z: 55(40.4%) vs O: 41(30.8%) Endocrine: Z: 1(0.7%) vs O: 0(0%) Hematic and lymphatic: Z: 3(2.2%) vs O: 5(3.8%) Metabolic and nutritional: Z: 5(3.7%) vs O: 14(10.5%) Musculoskeletal: Z: 8(5.9%) vs O: 8(6.0%) Nervous: Z: 82(60.3%) vs O: 64(48.1%) Respiratory: Z: 24(17.6%) vs O: 16(12.0%) Skin and appendages: Z: 14(10.3%) vs O: 10(7.5%) Special senses: Z: 8(5.9%) vs O: 6(4.5%) Urogenital: Z: 9(6.6%) vs O: 5(3.8%) Weight change (kg): Z +0.8 vs O +3.4, p<0.001

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Schering-Plough, Data on file. Study 7501012 DB RCT	NR	Asenapine vs Placebo Total Withdrawals: 59 vs 120 Withdrawals due to AEs: 16 vs 53	
Sethuraman, 2005 Sub-analysis of Tran 1997	NR	NR / NR	
Simpson, 2004 DB, multicenter, parallel, flexible-dose Inpatients	Scales used: Extrapyramidal Symptom Rating Scale, Barnes akathisia scale, Abnormal Involuntary Movement Scale (AIMS).	115 total withdrawals 5 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Simpson, 2005 (Continuation of Simpson, 2004) Funding: Pfizer, Inc	1) completion of 6 weeks' double-blind treatment with ziprasidone or olanzapine, 2) a CGI improvement score of ≤2 or a ≥20% reduction in Positive and Negative Syndrome Scale total score at acute-study endpoint, and 3) outpatient status.	ziprasidone mean dose 135.2 mg/day (range=78–162) olanzapine 12.6 mg/day (range=5–15) 6 months	NA	NR
Sirota, 2006 RCT, DB(?)	PANSS negative subscale score ≥15; SANS total score ≥60. Excluded due to: concurrent Axis 1 DSM-IV diagnosis, history of seizure disorder, al clinically significant medical condition that would interfere with evaluations or efficacy or tolerability, pregnancy, use of depot antipsychotics within 1 dosing interval, participation in another investigational drug trial w/in 30 days for study entry.	olanzapine 5-20 mg/day quetiapine 200-800 mg/day Titration schedule: olanzapine - day 1-5: 5 mg/day; day 6-10: 10 mg/day; day 11-end of study: 15 mg/day; up to 20 mg/day permitted during this period of sufficient response not achieved quetiapine - day 1: 50 mg/day; day 2: 100 mg/day: day 3-4: 200 mg/day; day 5-7: 300 mg/day; two wks: 400 mg/day; six wks: 600 mg/day; up to 800 mg/day permitted if sufficient response was not achieved	3-7 days to ensure dopamine receptor occupancy levels to return to baseline	biperiden; 1 pt received citalopram
Smith 2009 Open-label RCT single-center, psychiatric hospital, USA	Inclusion: inpatients with chronic DSM-IV schizophrenia or schizoaffective psychosis; age 18-65 years. Exclusion: currently treated with clozapine or antidiabetic drugs	Olanzapine (5-40, mean 25.2 mg/d) or risperidone (2-12, mean 6.1 mg/d) for 5 months	No wash-out period. Subjects switching to the assigned AAP were cross-tapered onto the new drug/ cross-tapered off baseline antipsychotic over a 1.5 to 4 week period.	Statins allowed if started 2+ months prior to study and no recent dosage changes

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Simpson, 2005 (Continuation of Simpson, 2004) Funding: Pfizer, Inc	Brief Psychiatric Rating Scale (BPRS) and the severity rating on the CGI; the Positive and Negative Syndrome Scale as well as positive and negative subscale scores and the rating on the Calgary Depression Scale for Schizophrenia. For safety- 1) vital signs, body weight, and body mass index; physical examination; clinical laboratory tests; and ECGs and 2) ratings on the Extrapyramidal Symptom Rating Scale, Barnes Rating Scale for Drug-Induced Akathisia, and Abnormal Involuntary Movement Scale.	NR - see earlier study		NA/NR/1236
Sirota, 2006 RCT, DB(?)	Assessment of reduction in SANS total and subscale scores (primary outcomes) and PANSS total and subscale scores (secondary outcomes) at weeks 1, 2, 4, 8 and 12 (final endpoint)	Mean age 37.2 yrs (SD 11.5) 80% male Ethnicity NR	Mean duration of illness: 14.5 yrs (SD 8.2) Previous antipsychotic use: >99%	NR/NR/40
Smith 2009 Open-label RCT single-center, psychiatric hospital, USA	Fasting assessments of glucose metabolism and prolactin at baseline and months 1, 2, and 5. Weight assessed monthly. Waist and hip circumference at baseline and month 5. PANSS total score measured monthly.	Mean age 41.9 98% male 74% Black	Olanzapine vs. risperidone: PANSS 64.04 (17.0) vs. 61.78 (13.7) Duration of illness 21.26 (11.42) vs. 23.17 (11.7) years Years hospitalized 2.47 (3.0) vs. 3.16 (5.25) BMI 29.96 (6.50) vs. 28.85 (5.71) N with glucose >100 mg/dL in last 3 years 5 vs. 7. 13/23 (56.5%) on olanzapine and 11/23 (48%) on risperidone were on same drug at baseline. 8/46 (17%) were not on either drug at baseline.	166/80/58

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Simpson, 2005 (Continuation of Simpson, 2004) Funding: Pfizer, Inc	0/0/126 when possible	Ziprasidone vs. olanzapine Change in LS mean (SE) BPRS -18.6 (2.1) vs. -20.5 (1.8) CGI-S -1.9 (0.2) vs. -2.0 (0.15) Total PANSS -32.6 (3.8) vs. -35.6 (3.3) Calgary -2.8 (0.7) vs. -3.0 (0.6)
Sirota, 2006 RCT, DB(?)	5/NR/unclear - presumably 40. Analysis based on "ITT" of all pts w/at baseline and at least one baseline measurement w/LOCF.	No SS between-group differences for SANS or PANSS scores (total and subscale) Median change in SANS from baseline at wk 12: Total SANS: O -11 v Q -12 Affective flattening and blunting: O -5 v Q -5 Attention impairment: O -2 v Q 0 Avolition: O -2 v Q -2 Alogia: O -1 v Q -2 Median change in PANSS from baseline at wk 12: Total PANSS: O -11.0 v Q -13.0 PANSS negative symptom score: O -5.0 v Q -5.0 PANNS positive symptom score: O -4.0 v Q -1.0
Smith 2009 Open-label RCT single-center, psychiatric hospital, USA	9/0/46 3 completed less than 2 months of drug treatment and were excluded from analysis	Olanzapine (n=23) vs. risperidone (n=23) Mean (±SEM) change from 5 months vs. baseline; P-values for change within group BMI 1.39±0.51; P<0.01 vs. 0.59±0.50; P=ns Prolactin fasting ng/mL -8.41±4.71; P=ns vs. 11.98±4.71; P<0.05 No differential drug effect on PANSS, results NR. There was no differential drug effect of olanzapine v. risperidone on change in BMI, weight, or waist circumference over time.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Simpson, 2005 (Continuation of Simpson, 2004) Funding: Pfizer, Inc	1) vital signs, body weight, and body mass index; physical examination; clinical laboratory tests; and ECGs and 2) ratings on the Extrapyramidal Symptom Rating Scale, Barnes Rating Scale for Drug-Induced Akathisia, and Abnormal Involuntary Movement Scale.	Ziprasidone vs. olanzapine Weight changes –0.82 kg vs. 4.97 kg BMI changes -0.59 vs 1.31 fasting insulin (1.0 µU/ml) vs. (2.0 µU/ml) Total cholesterol -1.0 mg/dl vs 13.0 mg/dl Mean QTc (Bazett correction) 407.1msec vs. 394.4 msec
Sirota, 2006 RCT, DB(?)	SAS, BAS and AIMS; other AEs 'recorded weekly'	Anxiety: O 7/21 (33.3%) v Q 7/19 (36.8%) Insomnia: O 6/21 (28.6%) v Q 6/19 (31.6%) Abdominal pain: O 2/21 (9.5%) v Q 1/19 (5.3%) Fever: O 2/21 (9.5%) v Q 1/19 (5.3%) Rhinitis: O 2/21 (9.5%) v Q 1/19 (5.3%) Conjunctivitis: O 2/21 (9.5%) v Q 0 Mean weight change at 12 wks: O +2.3kg v Q -0.9kg (p<0.01)
Smith 2009 Open-label RCT single-center, psychiatric hospital, USA	AEs of glucose metabolism were the primary outcomes of interest. Assessments: metabolic, anthropomorphic, clinical, chemical assessments	One patient assigned to olanzapine was withdrawn before 2 months of treatment due to abnormal glucose/lipid profile and excessive weight gain.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Simpson, 2005 (Continuation of Simpson, 2004) Funding: Pfizer, Inc	Ziprasidone vs. olanzapine Change in LS mean (SE) EPS rating scale -0.4 (0.3) vs. -0.7 (0.3) Barnes Rating Scale -0.2 (0.4) vs. -0.9 (0.3) AIMS score -0.07 (0.09) vs. -0.07 (0.07)	88 total withdrawals 25 due to AEs	
Sirota, 2006 RCT, DB(?)	No clinically significant changes in SAS, BAS or AIMS scores in either group. Akathisia: O 3/21 (14.3%) v Q 3/19 (15.8%) Parkinsonism: O 5/21 (23.8%) v Q 3/19 (15.8%) Use of biperiden: O 6/21 (28.6%) v Q 5/19 (26.3%)	5 (O=3; Q=2) total withdrawals 1 (O - jaundice) due to AEs	
Smith 2009 Open-label RCT single-center, psychiatric hospital, USA	NR	9 withdrawals 1 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Stroup, 2006 CATIE Phase 2T	Schizophrenia patients who had just discontinued treatment because patients who poorly tolerated their previous treatment, and discontinued their previous treatment because of inefficacy and did not want to consider treatment with clozapine, and discontinued their previous treatment independently of their doctor's recommendation.	Olanzapine 7.5–30 mg/day [N=66]; quetiapine, 200–800 mg/day[N=63]; risperidone, 1.5–6.0 mg/day [N=69]; ziprasidone, 40–160 mg/day [N=135]) up to a total of 18 months, overall or at least 6 months for this phase	Overlap in the administration of the antipsychotic agent that patients received before the study entry was permitted for the first four weeks after randomization to allow a gradual transition to study medication	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.
Stroup 2009 CATIE Phase 3	18 to 65 years, diagnosis of schizophrenia and appropriateness for oral antipsychotic medication	flexibile doses of monotherapies with oral aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, long acting injectable fluphenazine decanoate or a combination of any two of these treatments	Overlap in the administration of the antipsychotic agent that patients received in the prior phase was permitted for the first 4 weeks to allow a gradual transition to study medication	Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.
Stroup, 2007 CATIE Phase 1B	Patients who were assigned to treatment in phase 1 with perphenazine and who discontinued it then entered phase 1B	olanzapine, 7.5–30.0 mg/day quetiapine 200–800 mg/day risperidone 1.5–6.0 mg/day 18 months or discontinuation	Overlap in the administration of the antipsychotic agent that patients received before the study entry was permitted for the first four weeks after randomization to allow a gradual transition to study medication	Concomitant medications were permitted throughout the trial, except additional antipsychotics

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Stroup, 2006 CATIE Phase 2T	The primary outcome measure was time until treatment discontinuation due to all causes; key secondary outcome was the reason for treatment discontinuation as judged by the study doctor. Additional secondary efficacy outcomes included scores on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression scale (CGI), which were collected at study baseline and after 1, 3, 6, 9, 12, 15, and 18 months of study	Mean age=40.8 years 69% male 66% white 30% black/African American 3% All other race groups 13% Hispanic	patients who discontinued the previous phase - "patient decision" (18%, N=81 of 448). intolerability: 87% [N=168 of 193]; inefficacy: 58% [N=184 of 318]).	1493/1052/444
Stroup 2009 CATIE Phase 3	Primary outcome: treatment discontinuation for any cause PANSS and CGI scores collected at baseline and at 1,3,6,9, 12, 15 and 18 months of study	Mean age: 40.5 years (SD11.0) 70% male 67% white 30% African american 3% other	Years since first antipsychotic medication prescribed, Mean (SD) Aripiprazole: 11.8 (9.6) Clozapine: 8.3 (8.5) Olanzapine: 15.1 (10.2) Quetiapine:15.9 (10.5) Risperiodne: 16.1 (11.4) Ziprasidone: (13.9 (11.1)	eligible:410 Enrolled: 270
Stroup, 2007 CATIE Phase 1B	The primary outcome measure was time until treatment discontinuation due to all causes; key secondary outcome was the reason for treatment discontinuation as judged by the study doctor. Additional secondary efficacy outcomes included scores on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression scale (CGI), which were collected at study baseline and after 1, 3, 6, 9, 12, 15, and 18 months of study	Mean age=40.8 years 77% male 65% white 33% black/African American 3% Asian 14% Hispanic	patients who discontinued perphenazine in phase 1 because of inefficacy (55 of 65, 85%) intolerability (37 of 40, 93%) "patient decision" (21 of 77, 27%).	1894/192/115

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Stroup, 2006 CATIE Phase 2T	395 withdrawn of which 106 were taken out because of changed protocol./289 LTF/338 analyzed	Median time until treatment discontinuation for any reason (months) olanzapine=6.3 vs risperidone=7.0 vs quetiapine=4.0 months vs ziprasidone=2.8 Hazard ratios (95% CI) for pair-wise comparisons: olanzapine vs risperidone=1.02 (0.67 - 1.55) p = NR olanzapine vs quetiapine=0.65 (0.43 - 0.97) p< 0.05 olanzapine vs ziprasidone=0.61 (0.43 - 0.87) p< 0.01 risperidone vs quetiapine =0.64 (0.43 - 0.95) p< 0.05 risperidone vs ziprasidone =0.60 (0.42 - 0.85) p< 0.01 quetiapine vs ziprasidone =0.94 (0.67 - 1.31) p = NR PANSS Total Score differences at 3 months olanzapine vs quetiapine=6.8 (p=0.005 and ziprasidone = 5.9 (p=0.005)
Stroup 2009 CATIE Phase 3	106/NR/Differen	Mean (SD) change in PANSS score at 6 mo from baseline : Aripiprazole(N=18) -13.7 (14.0), p<0.001 Clozapine (N=24)-13.3 (21.3)p=0.006 Olanzapine (N=30) -9.7 (16.3), p=0.003 Quetiapine(N=23) -7.0 (19.6), p=0.100 Risperidone (N=24) -8.1 (13.9), p=0.009 Ziprasidone (N=21) -3.1 (15.7), p=0.371
Stroup, 2007 CATIE Phase 1B	77(68%)/0/114	Median time until treatment discontinuation for any reason (months) olanzapine=7.1 vs quetiapine=9.9 vs risperidone=3.6 months Hazard ratios (95% CI) for pair-wise comparisons: olanzapine vs quetiapine=0.97 (0.53 - 1.75) p= 0.91 olanzapine vs risperidone=0.53 (0.31 - 0.91) p= 0.02 quetiapine vs risperidone=0.55 (0.32 - 0.95) p= 0.04 Discontinuations due to lack of efficacy (% pts) olanzapine=18 vs quetiapine=34 vs risperidone=34 months Hazard ratios (95% CI) for pair-wise comparisons: olanzapine vs quetiapine=0.55 (0.22 - 1.39) p= 0.21 olanzapine vs risperidone=0.36 (0.14 - 0.92) p= 0.04 quetiapine vs risperidone=0.66 (0.30 - 1.45) p= 0.30 PANSS Total Score Change at 3 months olanzapine=9.6 vs quetiapine=6.5 vs risperidone=5.3 CGI severity change in score at 3 months olanzapine=0.4 (vs. risperidone p = 0.03) vs quetiapine=0.5 (vs. risperidone p = 0.005) vs risperidone=0.1

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Stroup, 2006 CATIE Phase 2T	AIMS global severity Barnes Akathisia Rating Scale Simpson-Angus Extrapyramidal Signs Scale Voluntary report of moderate to severe adverse event by systemic inquiry	olanzapine vs risperidone vs quetiapine vs ziprasidone (%pts) (p-values are NS unless otherwise specified and come from a test with df=3 comparing all treatment groups) Any serious AE: 6% vs 11% vs 8% vs 15% Insomnia: 13% vs 23% vs 16% vs 31%, p=0.01 Hypersomnia/sleepiness: 28% vs 22% vs 23% vs 13% Urinary hesitancy/dry mouth/constipation: 21% vs 21% vs 27% vs 17%p=0.002 Sex drive/sexual arousal/sexual orgasm: 17% vs 29% vs 11% vs 15% Gynecomastia/galactorrhea: 1% vs 5% vs 0 vs 1% Incontinence/nocturia: 1% vs 3% vs 4% vs 4% Orthostatic faintness: 7% vs 6% vs 13% vs 4% Skin rash: 2% vs 6% vs 8% vs 4% Weight gain from baseline ≥ 7%: 27% vs 13% vs 13% vs 6% Weight change (mean lb): 1.3 vs -0.2 vs 0.1 vs -1.7
Stroup 2009 CATIE Phase 3	Safety and tolerability outcomes includes incidence of serious adverse events, treatment emergent adverse events, changes in weight, measures of neurologic side effects and laboratory analytes	Aripiprazole vs clozapine vs olanzapine vs quetiapine vs risperidone vs ziprasidone Weight gain>7%: 7% vs 32% vs 23% vs 16% vs 14% vs 7%,p=0.031
Stroup, 2007 CATIE Phase 1B	AIMS global severity Barnes Akathisia Rating Scale Simpson-Angus Extrapyramidal Signs Scale Voluntary report of moderate to severe adverse event by systemic inquiry	Olanzapine vs quetiapine vs risperidone (%pts) (p-values are NS) Any serious AE: 5% vs 11% vs 8% Insomnia: 10% vs 18% vs 16% , Hypersomnia/sleepiness: 26% vs 42% vs 16% Urinary hesitancy/dry mouth/constipation: 33% vs 16% vs 24% Decreased sex drive/sexual arousal/sexual orgasm: 23% vs 18% vs 13% Gynecomastia/galactorrhea: 3% vs 0 vs 0 Menstrual irregularities: 10% vs 13% vs 11% Incontinence/nocturia: 0% vs 3% vs 3% Sialorrhea: 0% vs 3% vs 8% Orthostatic faintness: 8% vs 18% vs 3% Skin rash: 8% vs 3% vs 11% Weight gain from baseline ≥ 7%: 36% vs 24% vs 14% Weight change (mean lb): 11.9 vs 2.0 vs 2.8

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Stroup, 2006 CATIE Phase 2T	AIMS severity score ≥ 2: 9% vs 8% vs 17% vs 10% Barnes score ≥ 3: 6% vs 3% vs 6% vs 5% Simpson-Angus mean score ≥ 1: 4% vs 12% vs 7% vs 4%	289 withdrawals 40 due to AE	
Stroup 2009 CATIE Phase 3	Aripiprazole vs clozapine vs olanzapine vs quetiapine vs risperidone vs ziprasidone AIMS severity index ≥2: 9% vs 8% vs 0% vs 105 vs 19% vs 12%, p=0.231 Barnes Global clinical assessment ≥ 3: 0% vs 3% vs 3% vs 7% vs 3% vs 15%, p=0.201 Simpson-Angus EPS mean scale score≥ 3% vs 7% vs 3% vs 10% vs 3% vs 4%p= 0.493	Aripiprazole vs clozapine vs olanzapine vs quetiapine vs risperidone vs ziprasidone Total withdrawals: 33% vs 46% vs 41% vs 36% vs 44% vs 41% (P=NS between groups) Withdrawals due to adverse events: 3% vs 16% vs10% vs 6% vs 6% vs 8% (P=NS between groups)	
Stroup, 2007 CATIE Phase 1B	AIMS severity score ≥ 2: 7% vs 12% vs 0% Barnes score ≥ 3: 0 vs 0% vs 0 Simpson-Angus mean score ≥ 1: 50 vs 0% vs 0	Total withdrawals 77 Due to AEs 17	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Suzuki, 2007 Open label RCT Japan	Older than 18 years and were required to score more than 54 points in the 18-item Brief Psychiatric Rating Scale BPRS.	First assigned to Olanzapine (N=26) First assigned to Quetiapine (N=26) First assigned to Risperidone (N=26) OLZ→QTP→RIS, OLZ→RIS→QTP, QTP→OLZ→RIS, QTP→RIS→OLZ, RIS→OLZ→QTP, RIS→QTP→OLZ. Up to 8 weeks each	NR	Lorazepam
Swartz, 2007 CATIE Phase 1 Quality of Life subgroup (n=455)	Patients who completed the Quality of Life Scale at baseline of Phase 1 and were available at the primary 12-month endpoint (n=455)	see above	see above	see above
Tollefson, 1999a; Tollefson, 1999b (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Depression, Mood disturbance, QoL	Diagnosis: schizophrenia, schizophreniform or schizoaffective disorders (DSM-IV), age 18-65, Min score of 42 on BPRS as extracted from PANSS (items 1-7); inpatient or outpatient	olanzapine: 10–20 mg/d mean dose: 17.2 mg/d risperidone: 4–12 mg/d mean dose: 7.2 mg/d Duration: 28 weeks	Washout: 2–9 days	benzodiazepines (limited use for agitation), chloral hydrate, diperiden or benztropine (up to 6mg/d) for treatment of EPS only

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Suzuki, 2007 Open label RCT Japan	Baseline and Weekly - BPRS and a clinical status good enough to be discharged for 66 inpatients and a successful continuation therapy with the same antipsychotic agent for more than 6 months for 12 outpatients. Drug-Induced Extra-Pyramidal Symptoms Scale (DIEPSS), the Clinical Global Impression (CGI: Severity of Illness, SOI and Global Improvement, GI) and the Global Assessment of Functioning (GAF)	Mean age 44.9 45% male Ethnicity NR	85% inpatients BPRS 72.6 (SD 8.5) DIEPSS 5.59 (SD 5.15) Duration of illness 17.0 (SD 11.7)	78 enrolled
Swartz, 2007 CATIE Phase 1 Quality of Life subgroup (n=455)	Change from baseline in Quality of Life Scale score	Mean age=41.9 years 75.8% male 62% white	Alcohol abuse=29% Drug abuse=20.4%	1493/1440/455
Tollefson, 1999a; Tollefson, 1999b (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Depression, Mood disturbance, QoL	PANSS (total, positive, negative, general psychopathology and depression) Heinrichs-Carpenter QOL Scale Measured weekly x 8 wks, then every 4 wks	Mean age 36 65% male 75% white	82% diagnosis = schizophrenia mean length of current episode: 154 days 80% had <4 prior episodes Prominent negative symptoms: 80%	NR/NR/339

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Suzuki, 2007 Open label RCT Japan	7 dropouts	Thirty-nine patients (50%) responded to the first agent (OLZ, n=16; QTP, n=9; RIS, n=14), 14 to the second agent (OLZ, n=6; QTP, n=5; RIS, n=3), and only two to the third agent (RIS alone). Sixteen patients (21%) failed to respond to all three atypical antipsychotics. Results for first arm only BPRS Baseline to endpoint Olanzapine 71.6 to 56.6 vs Quetiapine 71.4 to 60.6 vs Risperidone 72.6 to 58.6 Global assessment of functioning Baseline to endpoint Olanzapine 30.2to 44.4 vs Quetiapine 31.6 to 40.8 vs Risperidone 30.6 to 42.7 Severity of illness Baseline to endpoint Olanzapine 5.62 to 4.75 vs Quetiapine 5.6 to 4.98 vs Risperidone 5.64 to 4.91 Global improvement Olanzapine 3.06 vs Quetiapine 3.55 vs Risperidone 3.13
Swartz, 2007 CATIE Phase 1 Quality of Life subgroup (n=455)	NA/NA/455	Mean change in Quality of Life Scale (p-value represents within-group difference from baseline) Olanzapine (n=145): 0.19, p<0.05 Perphenazine (n=74): 0.19, p=NS Quetiapine (n=82): 0.09, p=NS Risperidone (n=107): 0.26, p<0.01 Ziprasidone (n=47): 0.26, p=NS Paired comparisons P vs O vs Q vs R: F=0.59, p=0.62 O vs Q vs R: F=0.64, p=0.53
Tollefson, 1999a; Tollefson, 1999b (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Depression, Mood disturbance, QoL	161/11/339	Overall Results: see Tran 1997 (HTA report tables) PANSS Mood item (scored 1-7): At 8 wks mean change: olanzapine 1.13 risperidone 0.85 (p=0.006) At 28 wks: olanzapine > risperidone (p=0.004, data not reported) PANSS Depression Cluster (PDC): At 8 wks: olanzapine: 59% improvement vs risperidone: 45% improvement (p=0.045) Of those with >/= 20% improvement in total PANSS, Kaplan-Meier analysis of maintenance of response to 28 wks: olanzapine > risperidone (p=0.001) Relapse Risk (from wk 8 to wk 28) If change from baseline < 7 points PDC: NS difference If change from baseline >/= 7 points: RR R vs O 8.55 (95% CI 2.99 to 24.47)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Suzuki, 2007 Open label RCT Japan	Body weight, blood pressure, and pulse were also monitored.	3 serious adverse events 1 risperidone neuroleptic malignant syndrome 1 olanzapine minor episode of cerebrovascular accident 1 quetiapine acute obstructive suppurative cholangitis owing to cholelithiasis
Swartz, 2007 CATIE Phase 1 Quality of Life subgroup (n=455)	NR	NR
Tollefson, 1999a; Tollefson, 1999b (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Depression, Mood disturbance, QoL	See Tran 1997	See Tran 1997

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Suzuki, 2007 Open label RCT Japan	Drug-induced extrapyramidal rating scale Baseline to endpoint Olanzapine (n=50) 5.26 to 5.38 Quetiapine (n=45) 5.98 to 5.64 Risperidone (n=50) 6.10 to 6.62	7 withdrawals Due to AEs NR	
Swartz, 2007 CATIE Phase 1 Quality of Life subgroup (n=455)	NR	N/A	
Tollefson, 1999a; Tollefson, 1999b (Tran, 1997 sub-analysis) RCT, multicenter, multinational (6 European, South Africa and US) Post-hoc Analysis of Depression, Mood disturbance, QoL	NR	See Tran 1997	Further analysis presented to show relationship of PANSS-mood items and QLS.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Tollefson, 2001	Schizophrenia Diagnosis: DSM-IV	olanzapine 15 mg/d, after first 2 weeks 15–25 mg/d mean 21 mg clozapine fixed dose escalation from 25 to 200 mg/d during days 1–8 of therapy; after first 2 weeks, 200–600 mg/d mean 303 mg Duration: 18 weeks	2–9 days	benzodiazepine (up to 40 mg daily diazepam equivalent or 8 mg lorazepam equivalent) for agitation, choral hydrate for insomnia, and biperiden or benztropine mesylate (up to 4 mg daily) for EPS permitted
Tran, 1997 Edgell, 2000	Diagnosis: schizophrenia, schizophreniform or schizoaffective disorders (DSM-IV), age 18-65, Min score of 42 on BPRS as extracted from PANSS (items 1-7); inpatient or outpatient	olanzapine, 10–20 mg/day; risperidone, 4–12 mg/	Washout: 2–9 days	benzodiazepines (limited use for agitation), chloral hydrate, diperiden or benztropine (up to 6mg/d) for treatment of EPS only

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Tollefson, 2001	PANSS Total (positive; negative subscale) CGI-S; BPRS total BPRS+ CGI-S;PANSS total score (≥20%;≥30%;≥40%;≥50% improvement; no improvement) EPS rating scales: SAS total; AIMS non-global total; BAS global score	Mean age (SD): 38.6 (10.6) years 63.9% male Ethnicity NR	Schizophrenia subtypes: catatonic 3/180; disorganized 34/180; paranoid 101/180; undifferentiated 34/180; residual 8/180 Schizophrenia course: residual symptoms 81/180; no residual symptoms 3/180; continuous 92/180; in partial remission 2/180; other pattern 2/180	NR/NR/180 olanzapine: 90 clozapine: 90
Tran, 1997 Edgell, 2000	PANSS total (primary) and positive, negative, general psychopathology and depression item; the 18-item BPRS total extracted from the PANSS; the Clinical Global Impressions-Severity of Illness Scale (CGI-S); Scale for the Assessment of Negative Symptoms (SANS); quality of life was assessed with the Quality of Life Scale Timing: weekly during the first 8 weeks of double-blind therapy and every 4 weeks thereafter	Mean age=36.21 64.9% male 74.6% white	81.7% diagnosis of schizophrenia 55.5% paranoid subtype Course of illness 39.8% continuous 34.5% episodic with inter-episode residual symptoms Age of onset of illness: 23.7 years Length of patients' current episodes: 153.8 days 80.4% had less than 10 previous episodes before entry into the study 41.9% were inpatients	NR/NR/339 olanzapine 172 risperidone 167

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Tollefson, 2001	olanzapine 36/2/90 clozapine 37/2/90	PANSS total (positive; negative subscales). Final equals change from baseline: Olanzapine: (n= 89) –25.6,25.5(–6.8,7.6;–7.1,7.4) Clozapine: (n= 87) –22.1,23.1,p= 0.888 (–6.4,7.2;–5.6,6.9) CGI-S;BPRS total. Final equals change from baseline: Olanzapine: (n= 89) –1.1,1.2;–15.2,15.3 Clozapine: (n= 87) –0.9,1.1;–14.0,13.3 BPRS+ CGI-S; PANSS total score (≥20%;≥30%;≥40%;≥50% improvement; no improvement): Olanzapine: (n= 89) 34/89;53/89;41/89;24/89;9/89;11/89 Clozapine: (n= 87) 30/87;47/87;28/87;14/87;9/87;14/87
Tran, 1997 Edgell, 2000	Withdrawn=161 (47.5%)/Lost to fu=11 (3.2%)/analyzed=331 olanzapine 166 risperidone 165	Olanzapine, risperidone, p-value Mean changes: PANSS Total: -28.1, -24.9, p=NS PANSS positive: -7.2, -6.9, p=NS PANSS negative: -7.3, -6.2, p=NS PANSS general psychopathology: -13.5, -11.8, p=NS PANSS depression item: -1.1, -0.7, p=0.004 BPRS total score: -17.0, -15.2, p=NS SANS summary score: -4.3, -2.9, p=0.020 CGI-S score: -1.1, -1.0, p=NS Improvement in PANSS total score ≥20%: 102 (61.5%), 104 (63%), p=NS ≥30%: 88 (53%), 72 (43.6%), p=NS ≥40%: 61 (36.8%), 44 (26.7%), p=0.049 ≥50%: 36 (21.7%), 20 (12.1%), p=0.020 Mean changes in Quality of Life Scale scores: Total score: 13.4, 8.8, p=NS Common objective and activities: 1.6, 1.2, p=NS Instrumental role: 1.7, 1.1, p=NS Interpersonal relations: 5.4, 2.8, p=0.011 Intrapsychic foundation: 4.8, 3.7, p=NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Tollefson, 2001	AMDP-5 solicited adverse events scale	Olanzapine: somnolence 12/90; agitation 10/90; headache 10/90; insomnia 7/90; constipation 6/90; weight gain 6/90; anxiety 5/90; rhinitis 5/90; dry mouth 4/90 (p = 0.043); vomiting 4/90; influenza syndrome 3/90; asthenia 2/90; increased salivation 2/90, sweating 2/90; dizziness 1/90; fever 1/90; leucopenia 1/90; nausea 1/90 Clozapine: somnolence 22/90; agitation 4/90; headache 5/90; insomnia 3/90; constipation 17/90 (p = 0.014); weight gain 6/90; anxiety 5/90; rhinitis 3/90; vomiting 5/90; influenza syndrome 5/90; asthenia 6/90; increased salivation 26/90 (p < 0.001); sweating 5/90; dizziness 8/90 (p = 0.017); fever 5/90; leucopenia 5/90; nausea 10/90 (p = 0.005); tooth disorder 4/90 (p = 0.043) AMDP-5 solicited adverse events scale (statistically significant): Olanzapine: drowsiness 23/89; hypersalivation 13/89; dry mouth 24/89 (p = 0.019) dizziness 6/89; increased perspiration 8/89; hypotonia 2/89; tardive dyskinesia 5/89 (p = 0.026); Clozapine: drowsiness 41/86 (p = 0.003) hypersalivation 54/86 (p < 0.001); dry mouth 11/86; dizziness 26/86 (p = 0.001); increased perspiration 19/89 (p = 0.016); hypotonia 9/86 (p = 0.025); tardive dyskinesia 0/86 Mean weight change (SD): olanzapine 1.8 (5.0) kg; clozapine 2.3 (4.9) kg – no significant difference Mean decrease in orthostatic blood pressure (SD): olanzapine 0.5 (14.5) mmHg; 3.7 (18.1) mmHg – no significant difference
Tran, 1997 Edgell, 2000	Adverse events were detected by clinical evaluation and spontaneous report at each visit and mapped, classified, and recorded using a system based on the U.S. Food and Drug Administration Coding Symptoms and Thesaurus for Adverse Reaction Terms (CPSTART). In addition, adverse events were solicited by the investigative site using the 40-item Association for Methodology and Documentation in Psychiatry (AMDP-5) adverse event questionnaire. EPS, akathisia and dyskinesia were further assessed with the SAS, BAS, AIMS	Olanzapine, risperidone, p-value Mean change in weight (kg): 4.1, 2.3, p=0.015 Corrected QTc interval prolongation: -4.9 vs 4.4, p=0.019 Prolactin concentrations (% pts with elevation above standard reference ranges): 51.2%, 94.4%, p<0.001 Hospitalization rate (days/month): 3.9, 4.5, p=NS Weight gain: olanzapine > risperidone (data nr, p-value nr) Nausea, amblyopia, extrapyramidal syndrome, increased salivation, suicide attempt, abnormal ejaculation, back pain, creatine phosphokinase increases, and urinary tract infection: risperidone > olanzapine (data nr, p-value nr) Solicited treatment-emergent adverse events (AMDP-5) Backache: 11 (6.6%), 22 (13.3%), p=0.040 Blurred vision: 16 (9.6%), 34 (20.6%), p=0.005 Breathing difficulties: 12 (7.2%), 24 (14.5%), p=0.031 Delayed ejaculation: 3 (1.8%), 12 (7.3%), p=0.016 Early waking: 20 (12%), 40 (24.2%), p-0.004 Increased dreams/nightmares: 19 (11.4%), 32 (19.4%), p=0.043

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Tollefson, 2001	EPS rating scales: SAS total; AIMS non-global total; BAS global score. Final equals change from baseline Intervention: (n = 88) –3.2, 4.8; –0.8, 2.2; –0.3, 0.9 Control: (n = 84) –1.4, 3.3 (p = 0.006); –0.7, 2.5; –0.4, 1.0	olanzapine 36/90 (40%) Due to AE 4 (4.4%) clozapine 37/90 (41%) Due to AE 13 (14.4%)	General comments: Using 'absolute' observed group mean changes from baseline, difference in means was 3.5 units in favor of olanzapine, and one-sided lower 95% confidence limit, –2.2, indicating no clinical difference between treatments. Using 'adjusted' group mean changes from baseline, difference in means was 3.8 units in favor of olanzapine and one-sided lower 95% confidence limit,–1.9. Post-hoc ANCOVA: adjusted endpoint least squares means, 80.3 olanzapine;83.4 clozapine, with one-sided CI of –3.7
Tran, 1997 Edgell, 2000	Olanzapine, risperidone, p-value Dystonic events: 1.7%, 6%, p=0.043 Parkinsonian events: 9.9%, 18.6%, p=0.022 Any EPS event: 18.6%, 31.1%, p=0.008 Akathisia events: 9.9%, 10.8%, p=NS Dyskinetic events: 2.3%, 3%, p=NS Residual events: 1.7%, 0.6%, p=NS Treatment-emergent dyskinetic symptoms (categorical analysis of AIMS according to Schooler and Kane criteria): 4.6%, 10.7%, p=0.049	olanzapine, risperidone, p-value Withdrawals: 73 (42.4%), 88 (52.7%), NS Withdrawals due to adverse events: 17 (9.9%), 17 (10.2%), NS	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
van Bruggen, 2003 Inpatients	Adolescents/young adults aged 16-28, first or second psychotic episode, schizophrenia, schizophreniform, schizoaffective disorder	6-10 week study Median doses: olanzapine: 15 mg/day, risperidone: 4 mg/day	NR	Antidepressants, benzodiazepines, mood stabilizers, anticholinergics
van Nimwegen, 2008 DB RCT Netherlands 4 center	Male and female; 18 to 30 years old, w/ schizophrenia, schizoaffective disorder, or schizophreniform disorder based on the Structured Clinical Interview for the DSM-IV, patient version.	Olanzapine (5,10, 15, or 20 mg/d) n=59 Risperidone (1.25, 2.5, 3.75, or 5 mg) n=63 6 weeks	NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
van Bruggen, 2003 Inpatients	PANSS	Mean age: 21 Years 79% Male Ethnicity NR	Adolescents/young adults aged 16-28	NR/NR/44
van Nimwegen, 2008 DB RCT Netherlands 4 center	Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score, PANSS, and Calgary Depression Scale for Schizophrenia, all at baseline and 6 weeks	Mean age 24.6 yrs 91.3% male Ethnicity NR	90% schizophrenia, 6% schizophreniform disorder, 4% schizoaffective disorder Baseline Y-BOCS score overall mean, 5.3 $\pm$ 8.1 Baseline PANSS scores (62.9 $\pm$ 18.8 in olanzapine vs 65.8 $\pm$ 20.2 in risperidone) Baseline CDSS scores (3.1 $\pm$ 5.8 in olanzapine vs 2.8 $\pm$ 12.3 in risperidone)	Screened NR/ 201 eligible / 131 took one dose

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
van Bruggen, 2003 Inpatients	NR/NR/31	Mean change in scores from baseline to endpoint: PANSS Total: O: -15.1 vs R: -15.0 Positive Symptoms: O: -0.3 vs R: -3.2 Negative Symptoms: O: -1.9 vs R: -1.9 Depression Symptoms: O: 2.1 vs R: 0.7 Agitation/excitement: O: -0.7 vs R: 0.4 Disorganization: O: 1.1 vs R: 0.8 General psychopathology: O: -6.6 vs R: -6.3 Achievement of remission at Endpoint: O: 28% vs R: 11%
van Nimwegen, 2008 DB RCT Netherlands 4 center	9 / 9/ 122	Olanzapine vs. risperidone Y-BOCS total score total group (N = 122: –2.2 vs –0.3, z = –2.651, P < 0.01), Baseline Y-BOCS total score > 0 (n = 58: –5.1 vs –0.4, z = –2.717, P < 0.01), Baseline Y-BOCS total > 10 (n = 29: –7.1 vs –0.6, z = –2.138, P = 0.032).

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
van Bruggen, 2003 Inpatients	Barnes Akathisia Scale (BAS), Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), 40-item Association for Methodology and Documentation in Psychiatry (AMDP-5)	Somnolence: O: 25% vs R: 66% Excessive thirst: O: 17% vs R: 53% Decreased libido: O: 17% vs R: 53% Excessive appetite: O: 42% vs R: 42% Akathisia: O: 33% vs R: 32% Headache: O: 33% vs R: 5% Dry Mouth: O: 25% vs R: 32% Dizziness: O: 25% vs R: 26% Difficulty falling asleep: O: 25% vs R: 26% Heaviness in legs: O: 25% vs R: 21% Menstrual difficulties: O: 25% vs R: 0% Hypersalivation: O: 17% vs R: 26% Increased perspiration: O: 17% vs R: 21% Palpitations: O: 17% vs R: 16% Blurred vision: O: 17% vs R: 16% Decreased appetite: O: 8% vs R: 16% Nausea: O: 8% vs R: 16% Vomiting: O: 8% vs R: 16% Breathing difficulties: O: 0% vs R: 16% Backache: O: 0% vs R: 16% Chills: O: 8% vs R: 16%
van Nimwegen, 2008 DB RCT Netherlands 4 center	NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
van Bruggen, 2003 Inpatients	Parkinsonism: O: 3% vs R: 3%	NR/NR	
van Nimwegen, 2008 DB RCT Netherlands 4 center	NR	9 withdrawals Due to AEs NR	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Volavka, 2001 DB, RCT Inpatients	Treatment-resistant, inpatients with DSM-IV diagnosis of schizophrenia, or schizoaffective disorder	14 week trial: clozapine (N=40): target for weeks 1-8: 500 mg/day, mean dose for weeks 9-14: 526.6 mg/day olanzapine (N=39): target for weeks 1-8: 20 mg/day, mean dose for weeks 9-14: 30.4 mg/day risperidone (N=41): target for weeks 1-8: 8 mg/day, mean dose for weeks 9-14: 11.6 mg/day haloperidol (N=37): target for weeks 1-8: 20 mg/day, mean dose for weeks 9-14: 25.7 mg/day	NR	Benztropine, propranolol, lorazepam, diphenhydramine hydrochloride, chloral hydrate

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Volavka, 2001 DB, RCT Inpatients	PANSS - hostility item-conducted at baseline and endpoint, PANSS, Extrapyramidal Symptom Rating Scale- conducted at baseline, 8 weeks and endpoint, Glucose levels taken at weeks 1, 8, 14, Total Aggression Severity (TAS), Plasma levels of prolactin, tested at weeks 1, 5, 8, 10,12, 14	Mean age: 40.33 years 84% Male 29% Caucasian 58.4% African-American 10.9% Hispanic 2% Asian-Pacific Islander	Schizophrenia: 135(86%) Schizoaffective disorder: 22(14%) 100% Male for testing of prolactin levels of plasma	NR/167/157

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Volavka, 2001 DB, RCT Inpatients	0/0/157 22 analyzed with Total Aggression Severity (TAS) 101 analyzed for glucose and cholesterol levels and weight gain 16 analyzed for prolactin levels of plasma	PANSS mean scores- hostility item: baseline vs endpoint clozapine: 2.68 vs 2.24 olanzapine: 2.35 vs 2.24 risperidone: 2.40 vs 2.49 haloperidol: 2.42 vs 2.95 Superiority over haloperidol at 14 weeks: clozapine: (p<0.007) olanzapine: (p<0.02) risperidone: (p=NR) haloperidol: (p=NR) Mean glucose level changes from baseline at 8 weeks and 14 weeks: clozapine: 17.1, 4.4; (p=NS) haloperidol: 8.4, 10.6; (p=NS) olanzapine: 1.9, 14.3; (p<0.02) risperidone: -1.3, 2.7; (p=NS) Mean change from baseline in cholesterol levels: 8 weeks, 14 weeks clozapine: 14.7, 16.3 mg/dl; (p=NS) haloperidol: -4.9, -4.4 mg/dl; (p=NS) olanzapine: 12.3, 20.1 mg/dl; (p<0.002) risperidone: 4.2, 9.2 mg/dl; (p=NS) Overall analysis of variance, effect of medication type on TAS: (p<0.013) Comparison of clozapine vs haloperidol: (p<0.007) Overall analysis of variance, effect of medication type on PANSS: (p=0.008) Negative relationship between TAS vs PANSS: (p=0.0004) Clozapine's efficacy increased with TAS, efficacy of risperidone and olanzapine decreased with TAS Olanzapine superior to haloperidol: (p<0.012), olanzapine superior to risperidone: (p<0.016), clozapine to haloperidol: (p<0.065)Risperidone: dose-dependent increased elevation of prolactin levels: (p<.05) Pair-wise comparisons significant increase in prolactin levels: Haloperidol vs clozapine: (p<.002) Haloperidol vs olanzapine: (p<.026) Olanzapine vs clozapine: (p=NS)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Volavka, 2001 DB, RCT Inpatients	Physical examination	Weight gain (kg), mean change from baseline olanzapine: 7.3 (7.6), p<0.0001 clozapine: 4.8(6.1), p<0.0003 risperidone: 2.4(6.3), p=0.09 haloperidol: 0.9(5.7), NS Association of cholesterol change and weight gain at endpoint four groups combined, p=0.0008 clozapine group, p=0.008 olanzapine group, p=0.035 after baseline cholesterol and weight were introduced as covariates in the analyses clozapine group, p<0.03 olanzapine group, p=0.06

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Volavka, 2001 DB, RCT Inpatients	Mean Extrapyramidal Symptoms scores from baseline: clozapine: at 8 weeks: 5.3; (p<0.03), at 14 weeks: 5.1; (p<0.005) olanzapine: at 8 weeks: 3.7; (p<<0.0008), at 14 weeks: 3.8; (p<0.0001) risperidone: at 8 weeks: 4.7; (p<0.002), at 14 weeks: 4.8; (p<0.005) haloperidol: at 8 weeks: 4.7; (p=NR), at 14 weeks: 4.4; (p=NR)	0 withdrawals 0 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Voruganti, 2007 RCT, rater blinded, multicenter	Established diagnosis of schizophrenia (DSM-IV) confirmed through administration of SCID; male or female aged 18-65; treated with first generation antipsychotic drugs and in need of switch to a second generation antipsychotic drug due to unresolved symptoms or distressing side effects. Exclusion criteria: developmental disorders, epilepsy or acquired brain injury and significant substance abuse comorbidity; lack of competence to consent	olanzapine (n=42): 17.2 mg/d (2.5) quetiapine (n=43): 612.8 (mg/d) Mean dosages, reported in baseline characteristics table only 12 months	Switch to newer medications achieved through an "overlap" strategy of gradual tapering of previous drug and gradual increase of the new medication	Rescue medications included benzodiazepines (lorazepam or clonazepam for anxiety and agitation or sleep difficulties); and adjunctive medications or anti-Parkinsonian medications were added, if felt necessary by physician, and were recorded for every patient
Wahlbeck, 2000 Open-label RCT	Diagnosis: schizophrenia (DSM-IV); Treatment-resistant: persistent psychotic symptoms for < 6 months while on medication from ≥ 2 different classes of antipsychotic drugs in doses ≥ 1000 mg/day chlorpromazine for > 6 weeks each; in addition, non-tolerance to haloperidol or non-response to haloperidol, > 40 mg/day	clozapine 400 mg/day for 2 weeks; flexible thereafter 600 mg/ day mean 385 mg/day risperidone, 6 mg/day for 3 days; flexible thereafter up to 10 mg/day mean 7.8 mg/day Duration: 10 weeks preceded by 6-week treatment with haloperidol, ≤ 50 mg/day if no history of previous treatment with haloperidol, > 40 mg/day, or haloperidol intolerance	1–3 days	biperiden (EPS) and lorazepam (anxiety) as required

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Voruganti, 2007 RCT, rater blinded, multicenter	PANSS, SSTICS, COGLAB, SIP, GAF, fasting blood glucose, weight, PETiT, DAI Evaluation battery administered at 1, 3, 6, 9, and 12 month points	Mean age yrs (SD): olanzapine: 41.33 (13.61) quetiapine: 38.72 (14.37) % male olanzapine: 83% quetiapine: 65% Ethnicity: NR	Duration of illness year (SD): olanzapine: 15.33 (11.31) quetiapine: 14.16 (11.76)	NR/NR/86
Wahlbeck, 2000 Open-label RCT	Leaving study early, relapse, Mental state (PANSS, CGI, PGI, Social Functioning Scale), Global assessment (GAF), Satisfaction with treatment (DAI-10)	Mean age 35.9 years; range, 24–55 years 55% male Ethnicity NR	Duration of illness, ~ 12 years, range 0.5–33 years; treatment resistant* illness	9000/90/20

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Voruganti, 2007 RCT, rater blinded, multicenter	1 post-randomization exclusion/85 analyzed	Clinical outcomes at 12 months (olanzapine vs. quetiapine) PANSS Total: 48.5 (9.9) vs. 49.4 (12.0); F=1.67 (df=1,79), P=0.28 Positive symptom subscale: 15.5 (4.58) vs. 11.4 (4.3); F=0.001 (df=1,79), P=0.97 Negative symptom subscale: 10.9 (3.15) vs. 14.8 (6.03); F=1.037 (df=1,79), P=0.31 General Psychopathology subscale: 22.3 (4.99) vs. 23.78 (6.2); F=1.772 (df=1,79), P=0.18 Cognitive cluster: 18.4 (5.41) vs. 15.64 (4.9); F=11.28 (df=1,79), P=0.02 DAI: 3.70 (1.50) vs. 6.26 (1.22); F=10.69 (df=1.79), P=0.002 PETiT (compliance subscale): 14.7 (3.1) vs. 16.34 (1.79); F=3.622 (df=1,67), P=0.06 BWISE: 10.95 (3.0) vs. 15.68 (3.1); F=52.73 (df=1,79), P=0.001 Functional outcomes at 12 months (olanzapine vs. quetiapine) SSTICS: 30.2 (18.2) vs. 19.4 (12.4); F=10.54 (df=1,71), P=0.002 Muller-Lyer's Visual task: 71.3 (10.6) vs. 67.2 (10.5); F=1.36 (df=1,81), P=0.56 Size estimation task: 2.88 (1.15) vs. 2.39 (0.62); F=0.84 (df=1,81), P=0.36 Backward masking task: 21.0 (4.82) vs. 26.17 (5.4); F=10.81 (df=1,81), P=0.01 Asarnow's task: 13.16 (2.3) vs. 15.39 (2.4); F=12.73 (df=1,81), P=0.01 Wisconsin card sorting test Total score: 63.0 (11.6) vs. 65.4 (12.6); F=34.74 (df=1,80), P=0.001 Perseverative errors: 17.19 (3.7) vs. 12.12 (3.5); F=65.74 (df=1,81), P=0.001 Random errors: 17.42 (4.2) vs. 11.39 (3.9); F=35.4 (df=1,81), P=0.001 Psychosocial functioning SIP: 65.7 (13.7) vs. 64.8 (14.6); F=0.431 (df=1,78), P=0.51 GAF: 64.72 (7.8) vs. 66.1 (8.05); F=0.881 (df=1,79), P=0.35
Wahlbeck, 2000 Open-label RCT	7/NR/19	20% improvement on PANSS: 50% clozapine, 67% risperidone (p=0.65) Hospital discharge: 60% clozapine, 78% risperidone (p=0.63) Mean Change in score (clozapine/risperidone, p-value) PANSS total: -10/-18 (NS) PANSS positive -4/-4 (NS) PANSS negative +1/-4 (p=0.056) CGI-S -0.6/-1.3 (NS) GAF: +4/+13 (NS) SFS: -13/-9 (NS) DAI: -0.8/-0.6 (NS)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Voruganti, 2007 RCT, rater blinded, multicenter	SAS, BAS, AIMS, UKU-SR	Outcomes at 12 months (olanzapine vs. quetiapine): UKU-SR: 21.9 (10.7) vs. 16.14 (8.8); F=2.674 (df=1,79), P=0.1 Weight gain (kg): 7.24 (2.43) vs. 2.84 (1.72); F=5.679 (df-1,79), P=0.02 # of Dysglycemics: 13 vs. 4, P=0.001
Wahlbeck, 2000 Open-label RCT	EPS symptoms (non-structured assessment)	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Voruganti, 2007 RCT, rater blinded, multicenter	Outcomes at 12 months (olanzapine vs. quetiapine) SAS: 0.37 (1.21) vs. 0.26 (1.24); F=0.035 (df=1, 79), P=0.85 AIMS: 0.92 (1.50) vs. 0.75 (1.06); F=0.024 (df=1,75), P=0.62 BAS: 0.05 (0.32) vs. 0.13 (0.47); F=2.239 (df=1,79), P=0.13	0 total withdrawals 0 due to AEs	
Wahlbeck, 2000 Open-label RCT	NR	6/20 ((30%) total withdrawals 3 (15%) due to AE 11% risperidone 18% clozapine	Pilot study.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Wang, 2006 RCT, DB	Diagnosed with schizophrenia spectrum disorder by SCID; judged by treating clinician to have been stable on conventional antipsychotic meds for at least 2 years; no previous therapeutic trial with an atypical antipsychotic medication; had a reason for switching to atypical antipsychotic medication including desire for improved efficacy, improved side effect profile and/or reduced risk of developing or worsening Tardive dyskinesia Exclusion criteria: unstable psychiatric, metabolic, hematologic, cardiovascular, hepatic or renal function	risperidone (n=19): mean dose 5.3 mg/d olanzapine (n=17): mean dose 13.8 mg/d	Phase (1) 3 week titration phase increasing study medication from 1 to 3 pills; Phase (2) 3 week combo phase during which both conventional antipsychotic and atypical antipsychotic co-administered; Phase (3) 3 week tapering phase where conventional antipsychotic was discontinued; Phase (4) 12 weeks of monotherapy with either risperidone or olanzapine	Not reported for 12 week outcome phase
Weiden 2009 Open-label RCT 2 sites, USA	Target population: first-episode schizophrenia patients. Assessment phase inclusion: Aged 16-40; inpatients or outpatients with a provisional diagnosis of schizophreniform disorder, schizophrenia, or schizoaffective disorder; and <=16 weeks of lifetime total AP medication exposure. Subjects were treated clinically for up to 12 weeks before being assigned into the RCT. RCT inclusion: SCID-confirmed diagnosis of schizophrenia, schizophreniform disorder, or schizoaffective disorder; clinical indication for a long-term maintenance AP treatment; clinical response to oral AP medication during evaluation. phase; willingness to attend outpatient treatment services; and completion of at least 1 baseline psychoeducation session that included a key family member.	Compares risperidone LA injectable to oral risperidone. Assessment phase: study clinicians could prescribe any AAP except clozapine. RCT: subjects were randomized to remain on oral medication, or to change to risperidone long-acting injection (RLAI); both groups received up to 2 psychoeducation sessions. Those on RLAI received an initial injection of 25 mg RLAI with initial overlap with oral risperidone for at least 3 weeks. The target maintenance dose for RLAI was 25 mg (allowable range 25-50 mg) every 2 weeks. Reports on the first 12 weeks of followup.	No wash-out period. Subjects on LA injectable received a minimum 3-week overlap of oral risperidone with initial injection of 25 mg.	Adjunctive therapies for affective or anxiety symptoms were allowed. Oral supplementation was permitted for acute exacerbations of positive symptoms, but long-term use (>4 weeks) of oral antipsychotic with risperidone LA injectable was not permitted in maintenance phase treatment.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Wang, 2006 RCT, DB	PANSS, CGI, SAS	Age mean yrs (SD): 47.0 (9.3) risperidone: 45.2 (9.9) olanzapine: 48.9 (8.4) % male (risperidone vs. olanzapine): 42.1% vs. 52.9%, P=0.74 % African American (risperidone vs. olanzapine): 89.5% vs. 82.4%, P=0.65 % White: 10.5% vs. 17.6%	Schizophrenia: 63.2% vs. 70.6% Schizoaffective: 36.8% vs. 29.4% PANSS score at baseline: risperidone 59.3 (12.4) olanzapine: 55.9 (13.4) P=0.46	NR/NR/36
Weiden 2009 Open-label RCT 2 sites, USA	Nonadherent behavior ('GAP') was defined as >=14 consecutive days of not taking antipsychotic medication. Adherence was measured by All-Source Verification, which uses prescription refill data for oral medication, clinical records of risperidone LA injectable administration, patient report, clinical notes, and family reports. Outcomes: adherence behavior between initial randomization and 12-week follow-up; time until initial GAP; proportion having at least 1 GAP within the initial 12-week follow-up period. Adherence attitude was measured by a blinded assessor using the Rating of Medication Influences (ROMI) scale at 12-week followup.	Median age 23 years 69% male 34% African American 57% Afro-Caribbean	At study entry, 81% (n=30) were on oral risperidone at study entry; 11% (n=4) on haloperidol; 5% (n=2) on olanzapine; 3% (n=1) on quetiapine.	74/46/37

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Wang, 2006 RCT, DB	13 withdrew; analysis based on ITT population (N=36) using LOCF	PANSS mean (SD) risperidone vs. olanzapine Total score Baseline: 59.3 (13.4) vs. 55.9 (13.7) Endpoint: 44.3** (9.8) vs. 46.9** (13.2) Factor Scores--Positive Baseline: 14.9 (5.3) vs. 14.0 (5.7) Endpoint: 10.4** (3.7) vs. 11.6* (4.9) Factor Scores--Negative Baseline: 16.4 (4.9) vs. 16.8 (4.0) Endpoint: 12.3** (3.7) vs. 13.3** (3.7) Disorganized thoughts Baseline: 14.1 (3.9) vs. 12.8 (3.9) Endpoint: 11.3** (2.6) vs. 10.7** (3.2) Uncontrolled hostility/excitement Baseline: 5.9 (2.0) vs. 5.3 (2.0) Endpoint: 4.4** (0.7) vs. 5.1 (1.7) Anxiety and depression Baseline: 8.1 (3.2) VS. 7.0 (3.0) Endpoint: 5.9** (2.8) vs. 6.2 (2.7) *Significantly lower than baseline (within group comparison, P<0.05) **Significantly lower than baseline (within group comparison, P<0.01)
Weiden 2009 Open-label RCT 2 sites, USA	0/0/37	26 assigned to risperidone LA injectable; 11 assigned to oral risperidone. 19 of 26 (73%) assigned to risperidone LA injectable accepted 9 (24%) of all 37 subjects experienced at least 1 GAP within 12 weeks after randomization. In ITT analysis there were no differences between RLAI and Oral groups on adherence: At least 1 GAP by week 12: 6/26 (23%) on RLAI vs. 3/11 (27%) on Oral; P=1.0 In analysis of actual treatment (where oral group includes subjects assigned to RLAI but declined), RLAI accepters were more likely to remain adherent than remaining Oral group. Risperidone LA injectable vs. oral: At least 1 GAP by week 12: 2/19 (11%) vs. 7/18 (39%); P=0.063 Kaplan-Meier analysis, %Adherence: 89%; 95%CI,64%-97% vs. 59%; 95%CI, 32%-78%; P=0.035 Medication adherence attitudes were similar between groups for either ITT or AAT comparison.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Wang, 2006 RCT, DB	EPS side effects assessed by SAS; body weight measured at each visit	Both risperidone and olanzapine patients exhibited significant weight increase during study. Risperidone patients gained 3.4 lbs (SD 6.2) (t=2.4, df=18, P<0.05) vs. 7.6 lbs (SD 9.6) increase in olanzapine patients (t=3.3, df=16, P<0.01). Comparison of weight increases between groups revealed significantly higher gain in olanzapine treated group at 16 wks (t=2.3, df=34, P<0.05), however at 22 wks this difference was no longer significant (t=1.6, df=34, P=0.12). No other AEs reported
Weiden 2009 Open-label RCT 2 sites, USA	NR	Reports that there was no side-effect distress in either group at 12 weeks.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Wang, 2006 RCT, DB	Simpson-Angus scores decreased in both groups comparably over course of study (F[5,204]=4.2, P<0.01).	13 (36%) total withdrawals risperidone: 8 olanzapine: 5 6 (16.7%) due to AEs risperidone: 4 olanzapine: 2	
Weiden 2009 Open-label RCT 2 sites, USA	NR	0 withdrawals 0 due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Weiden, 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals)	Men or women aged 18 to 55, DSM-IV schizophrenia or schizoaffective disorder outpatients status for ≥ 3 months; treatment with current antipsychotic within 25% of recommended dosage for ≥ 3 months with at least partial response (CGI-I score <4 since the initiation of current antipsychotic); inadequate response to or poor tolerability of current medication; and 8th grade reading level.	Flexible dose of ziprasidone though week 6 (40-160mg/d) Mean ziprasidone daily dose: 91mg for those switched from conventional antipsychotic; 90mg for those switched from olanzapine; 92mg for those switched from risperidone 6-week duration	1 of 3 ways drugs switched: Complete discontinuation: previous drug was stopped the day before the switch to Z; Immediate dose reduction: a 50% reduction in dosage of previous antipsychotic for the first wk of Z followed by discontinuation of previous starting wk 2 Delayed dose reduction: previous drug reduced by 50% starting on the fourth day of Z treatment and was discontinued by the second wk of Z treatment	Other psychotropic agents were not allowed (except for anti-EPS agents)
Wu, 2006 Wu, 2007 Randomized, unblinded, longitudinal study	Consistently referred patients, aged 18-45 with a first psychotic episode of schizophrenia diagnosed with DSM-IV criteria; to remain hospitalized for 8 weeks; had same diets throughout trial; no use of any antipsychotics or other recreational drugs before enrollment; not involved in weight reduction diets or programs. Exclusion criteria: pregnant or lactating; mental retardation; addictive disorder; specific systemic diseases or other medical conditions such as diabetes mellitus, dyslipidemia, cardiovascular diseases, and hypertension.	Clozapine (n=30): 200-400 mg/d Olanzapine (n=24): 10-20 mg/d Risperidone (n=29): 2-5 mg/d Sulpiride (n=29): 600-1,000 mg/d 8 week study duration	NR	Only trihexyphenidyl for EPS or lorazepam for insomnia or agitation was allowed on a needed basis

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Weiden, 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals)	PANSS and CGI were conducted by investigators or trained research assistants	Mean age: 37.6 years Age range: 18-61years 65.5% male Ethnicity: NR	Mean baseline PANSS total score Conventional: 67.5 (SD: 16.3) Olanzapine: 65.6 (SD: 16.7) Risperidone: 71.0 (SD: 19.0) Mean baseline CGI-S Conventional: 3.5 (SD: 0.74) Olanzapine: 3.5 (SD: 0.81) Risperidone: 3.7 (SD: 0.74)	NR/ NR/ 270
Wu, 2006 Wu, 2007 Randomized, unblinded, longitudinal study	BMI, WHR, fasting glucose, triglyceride, cholesterol, insulin, C-peptide, insulin resistance index at baseline and endpoint	Age, mean (SD) All: 34.87 (10.20) clozapine: 32.6 (8.4) olanzapine: 34.2 (10.3) risperidone: 33.4 (9.7) sulpiride: 32.9 (8.6) % female All: 50% clozapine: 53% olanzapine: 42% risperidone: 52% sulpiride:52% Ethnicity: NR (presumably 100% Chinese)	Schizophrenia, paranoid type clozapine: 47% olanzapine: 54% risperidone: 48% sulpiride: 48% Schizophrenia, catatonic type clozapine: 3% olanzapine: 0% risperidone: 4% sulpiride: 4% Schizophrenia, disorganized type clozapine: 7% olanzapine: 8% risperidone: 10% sulpiride: 7% Family history of type II diabetes clozapine: 10% olanzapine: 8.3% risperidone: 7% sulpiride: 7%	NR/NR/120

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Weiden, 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals)	Unclear: numbers analyzed changed depending on the test	All results were health indices
Wu, 2006 Wu, 2007 Randomized, unblinded, longitudinal study	8/112	Difference between baseline and endpoint of metabolic profiles (clozapine vs. olanzapine vs. risperidone vs. sulpiride): BMI (kg/cm2): 1.49 (0.20) vs. 1.11 (0.13) vs. 0.19 (0.12) vs. 0.66 (0.12); P=0.009 WHR: 0.02 (0.007) vs. 0.01 (0.005) vs. 0.007 (0.002) vs. 0.008 (0.003); P=ns FG (mmol/l): -0.07 (0.03) vs. -0.05 (0.01) vs. -0.12 (0.06) vs. - 0.03 (0.02); P=ns TG (mmol/l): 0.48 (0.07) vs. 0.39 (0.08) vs. 0.11 (0.05) vs. 0.17 (0.05); P=0.02 CHOL (mmol/l): 0.63 (0.18) vs. 0.75 (0.14) vs. 0.12 (0.07) vs. 0.21 (0.06); P=0.005 Ins (10*3 mU/L): 16.54 (1.65) vs. 14.14 (1.62) vs. 5.43 (1.41) vs. 6.79 (1.07); P=0.005 CP (pmol/l): 262.69 (41.63(vs. 225.78 (42.50) vs. 49.34 (29.55) vs. 61.00 (25.85); P=0.001 IRI: 3.45 (0.50) vs. 2.80 (0.36) vs. 1.12 (0.30) vs. 1.57 (0.29); P=0.007 Subgroup analyses based on gender (male:female) for clozapine vs olanzapine vs risperidone vs sulpiride (within-group between-gender p-values NS unless otherwise specified) TG (mmol/100 mL): 62.88:25.68 (p=0.007) vs 46.94:8.85 (p=0.002) vs 15.05:10.62 vs 12.40:28.34 (p=0.035) No other within-group gender differences for clozapine, olanzapine, or risperidone for any other metabolic parameters

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Weiden, 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals)	AEs incidence and severity were recorded throughout the study; vital signs and body weight were measured at baseline and weekly. EPS were assessed at baseline and at endpoint using the Simpson-Angus scale for Parkinsonism side effects and the Barnes Akathisia scale for akathisia. Metabolic and endocrine lab tests were performed at screening and endpoint	Mean body weight change in patients from baseline to week 6; p-values for baseline vs wk 6: Olanzapine (n=99): -1.8 kg (estimated from figure), p<0.0001 Risperidone (n=55): - 0.86kg, p<0.002 Conventional antipsychotics (n=102): +0.27kg, p=0.3 Median change in prolactin levels baseline to wk 6 (approximated from figure; p-values for baseline vs wk 6) Olanzapine (n=92) : -2 mg/ml, p=0.6 Risperidone (n=49): -32 mg/ml, p<0.0001 Conventional antipsychotics (n=81): -4 mg/ml, p<0.05 Median change in triglyceride levels baseline to wk 6; p-values for baseline vs wk 6: Olanzapine (n=91): -50 mg/dL, p<0.0001 Risperidone (n=50): -29 mg/dL, p<0.01 Conventional antipsychotics (n=82): -17mg/dL, p=NS (estimated from graph) Median change in total nonfasting cholesterol levels baseline to wk 6; p-values for baseline vs wk 6: Olanzapine (n=91): -21 mg/dL, p<0.0001 (estimated from graph) Risperidone (n=50): -18mg/dL, p<0.01 (estimated from graph) Conventional antipsychotics (n=82): - 3 mg/dL, p= NS (estimated from graph)
Wu, 2006 Wu, 2007 Randomized, unblinded, longitudinal study	NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Weiden, 2003 open-label CCT (3 separate open-label studies on switching to Z from O, R, or Typicals)	Mean Simpson-Angus scores: Significant % improvement after switching from: Conventional antipsychotics: 48% improvement, p<0.0001, effect size 0.493 Risperidone: 45% improvement, p<0.001, effect size: 0.381 Concomitant antiparkinsonian drug use decreased for patients who switched from conventional antipsychotics: 58% at baseline to 14.8% after 6 wks. Concomitant antiparkinsonian drug use decreased for prior risperidone pts from 26% to 8.6% at 6 weeks.	The studies were completed by 72%, 79%, and 79% of patients switched from conventional antipsychotics, olanzapine, and risperidone, respectively. Discontinuations due to AEs after switching from: Conventional antipsychotics: 11% Olanzapine: 6% Risperidone: 9%	
Wu, 2006 Wu, 2007 Randomized, unblinded, longitudinal study	NR	8 total withdrawals 0 withdrawals due to AEs	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Yamashita, 2004 Inpatients	Schizophrenia	Olanzapine: 2.5-20.0 mg/day Perospirone: 4.0-48.0 mg/day Quetiapine: 50.0-750.0 mg/day Risperidone: 1.0-12.0 mg/day	4 weeks	NR
Zhong, 2004 Poster Only RCT	Men or women, aged 18-65 years old, with a diagnosis of catatonic, disorganized, paranoid, or undifferentiated schizophrenia according to DSM-IV; PANSS total score of ≥ 60 at baseline (Day 1); a baseline score of ≥ 4 on one or more of the PANSS items for delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution; CGI-S score ≥ 4 at baseline	Quetiapine 50 mg/d, increased to 400 mg/d by day 5, then flexibly dosed in range of 200-880 mg/d (mean dose=525 mg) Risperidone 2 mg/d, increased to 4 mg/d by day 5, then flexibly dosed in range of 2-8 mg/d (mean dose=5.2 mg) Duration: 8 weeks Setting: hospitalized for ≥ 7 days following randomization	NR	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Yamashita, 2004 Inpatients	Pittsburgh Sleep Quality Index (PSQI), Positive and Negative Syndrome Scale (PANSS)	Mean age: 59.9 years 52.1% Male Ethnicity NR	100% In-patient Schizophrenia Diagnoses: Disorganized: 29(31.5%) Paranoid: 11(11.9%) Undifferentiated: 52(56.5%)	NR/92
Zhong, 2004 Poster Only RCT	PANSS total and subscale: change from baseline to Day 56; proportion of patients with CGI-C ratings of "much improved" or "very much improved" at the final assessment, and response rate, which was defined as the proportion of patients who achieved at least a 40% reduction on PANSS total and subscale scores at the end of treatment Timing: days 1, 4, 8, 15, 28, 42 and 56	Mean age 39.94 75.7% male 50.8% black 38.7% white 7.6% Hispanic 2.9% other ethnicity	Glucose (mg/dL): 99.7 Weight (kg): 86.6 Prolactin (ng/mL): 22.65 PANSS total scores: 92.5	NR/NR/673 quetiapine 338 risperidone 335

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Yamashita, 2004 Inpatients	NR	PSQI Results: Change in Score After Switched From Typical to Atypical Olanzapine vs Perospirone vs Quetiapine vs Risperidone Sleep quality: -.050 vs 0.2 vs -0.33 vs -0.35; P=.063 Sleep latency: -0.45 vs -0.22 vs -0.59 vs -0.35; P=.76 Sleep duration: -0.55 vs 0.69 vs -0.22 vs -0.25; .0009 Habitual sleep efficiency: -0.80 vs 0.47 vs -0.44 vs -0.65; P=.0024 Sleep disturbances: -0.20 vs 0.04 vs -0.11 vs -0.25; P=.36 Use of sleep medications: -0.05 vs 0.13 vs -0.07 vs -0.30; P=.50 Daytime dysfunction: -0.65 vs 0.21 vs -0.15 -0.30; P=.0018
Zhong, 2004 Poster Only RCT	351 (52.1%) withdrawn/analyzed nr	Change from baseline to endpoint for PANSS total scores: quetiapine=risperidone, p-value NR Proportions of patients with ≥ 40 reduction in PANSS total, positive, negative, and general pathology scores: quetiapine=risperidone, p-values NR CGI-C (% patients who were "much" or "very much" improved by Day 56): quetiapine=risperidone, p-values NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Yamashita, 2004 Inpatients	Patient self-report	NR
Zhong, 2004 Poster Only RCT	Change from baseline to the endpoint on the SAS, AIMS, BARS; the incidence of reported adverse events related to EPS and the incidence of treatment-emergent adverse events; and reporting of laboratory test results, vital sign measurements and clinically significant changes in weight, glucose, prolactin, and ECG results	Quetiapine, risperidone, p-values not provided Somnolence: 89 (26.3%), 66 (19.8%) Headache: 51 (15.1%), 56 (16.8%) Dizziness: 48 (14.2%), 32 (9.6%) Dry mouth: 41 (12.1%), 17 (5.1%) Agitation: 5 (17%), 3 (10%) Withdrawals due to somnolence: 2 (0.6%), 1 (0.3%) Withdrawals due to akathisia: 0, 4 (1.2%) Withdrawals due to dystonia: 0, 6 (1.8%) EPS-related adverse events: 43 (12.7%) vs 73 (21.9%), p<0.01 BARS improvement: quetiapine > risperidone, p-value nr SAS and AIMS improvement: quetiapine=risperidone Sexual adverse events: 2 (0.6%), 15 (4.5%), p-value nr Change in plasma prolactin (ng/mL) All patients: -11.5, +35.5, p<0.001 Females: -12, +63 (estimated from graph), p<0.001 Mean change in glucose levels (mg/dL): 3.9, 4.5 % pts with blood glucose levels ≥ 230: 1.8, 1.7 Mean change in weight (kg) : 1.6, 2.2 % pts with ≥ 7% gain: 10.4 vs 10.4

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Yamashita, 2004 Inpatients	NR	NR	
Zhong, 2004 Poster Only RCT	NR	Withdrawals due to adverse events (# patients; population analyzed nr): 20 vs 23	

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Zhong, 2006 R, DB, MC, flexible-dose non-inferiority study 66 centers in US. Inpatients (minimum of 7 days following randomization) then treated on an outpatient basis	18-65 years of age; schizophrenia (DSM-IV); total score ≥ 60 on PANSS; score of ≥4 on 1 or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, suspiciousness, or persecution; and CGI Severity or Illness score of ≥ 4 and clinical deterioration during the 3 weeks preceding randomization.	Quetiapine 200-800mg/day (titrated schedule) (mean doses: 525 mg/day) Risperidone 2-8 mg/day- (titrated schedule) (mean dose 5.2mg/day) x 8 weeks (Mean duration of treatment Q: 34.7 days vs. Q: 36.5 days)	1 week screening period prior to randomization	Anticholinergics PRN.. Lorazepam up to and not beyond day 3

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Zhong, 2006 R, DB, MC, flexible-dose non-inferiority study 66 centers in US. Inpatients (minimum of 7 days following randomization) then treated on an outpatient basis	Assessed at baseline and on days 4, 8, 15, 28, 42, and 56. Primary: PANSS Total Score week 8 or study withdrawal. Secondary outcomes: % of pts rated "very much" or "much" improved on the CGI-Change scale, proportion of pts achieving ≥ 40% reduction) in PANSS total and subscale scores; proportion of pts who had ≥ 30% reduction in PANSS total and subscale scores; and the change from baseline to final assessment in PANSS positive, negative, and general psychopathology subscale scores, cognitive assessments included measures of vigilance processing speed, verbal learning and delayed recall and verbal skill; social functioning (PEAT), social competence (SSPA)	Age, mean (SD), y Q: 40.2 (10.8); R: 39.6 (10.8) Males: Q: 77.1%, R:74.4% Race, n (%) White: Q: 130 (38.4), R 131 (39.1%) African American: Q: 171 (50.6); R: 171, (50.9) Hispanic: Q: 25 (7.3); R:26 (7.8) Other: Q: 12 (3.6) R: 7 (2.2)	Both groups were moderately to severely ill (mean BL PANSS total scores > 92 and CGI-Severity of Illness of 4.6).	872/NR/673

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Zhong, 2006 R, DB, MC, flexible-dose non-inferiority study 66 centers in US. Inpatients (minimum of 7 days following randomization) then treated on an outpatient basis	62/65/322 Withdrew consent: Q: 28 (8.3%); R: 34 (10.2%) Lost to follow-up: Q: 25 (7.4%); R: 40 (11.9%)	Efficacy: PANSS total scores: MITT patients (LOCF; p<.05),among completers (p<.01) , or when pts with significant protocol violations or deviations were excluded (p<.02). Change from Baseline in PANSS Total Score: LOCF: p=NS OC: p=NS % ≥ 40% reduction in PANSS Scores: PANSS total scores, positive, negative, general at endpoint: LOCF: p=NS; completers: p=NS % ≥ 30% reduction in PANSS Scores: Q: 27.4% R: 27.7%; p=NS Q vs. R: Difference Least squares Mean PANSS subscale at wk 8 and last Observation: LOCF for Positive Symptoms; p=.03 LOCF for negative, general psychopathology, anxiety, depression; p=NS Completers for positive, negative, general psychopathology, anxiety, depression; (all p=NS) CGI-C scores: 8 wk: % of pts rated "much" or "very much" improved for LOCF and completers: p=NS Cognitive measures: (multivariate analysis of covariance (controlling for BL score and site): p=NS PEAT or SSPA: p=NS Changes from baseline within each group in phonological fluency, trail making, verbal learning, vigilance, and SSPA, but not PEAT scores, were "statistically significant" (data not shown but published in Harvey P et al Am J Psychiatry. (In Press)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Zhong, 2006 R, DB, MC, flexible-dose non-inferiority study 66 centers in US. Inpatients (minimum of 7 days following randomization) then treated on an outpatient basis	Spontaneous reports of treatment-emergent at each visit, changes in weight, glucose and prolactin at week 8 or study withdrawal. EPS: SAS, AIMS, BARS	Q: (n=338) vs. R: (n=334) All AE: Q: 76.3% vs. R: 76.6% Serious AEs : Q: 14 (4.1%) vs. R: 9 (2.7%) Adverse Events Occurring in ≥ 5% of pts: Q n (%) vs. R n (%) Somnolence: 89 (26.3) vs. 66 (19.7), p=.044 Dry mouth 41 (12.1) vs. 17 (5.1), p<.01 Akathisia 13 (3.8) vs. 28 (.8.4), p=.016 Dystonia 1 (0.3) vs. 18 (5.4), p<.001 Headache, weight gain, dizziness, dyspepsia, nausea, pain, asthenia, agitation, pharyngitis, vomiting; all p=NS 8 wk Mean Prolactin levels change vs. BL (ng/mL) All patients: Q: -11.5 vs. R 35.5; p<.001 Mean Prolactin levels change from baseline for Females (ng/mL): Q:(n=42) -12.7 vs. R: (n=59) 60.9; p<.001 Mean Prolactin levels change from baseline for Men (ng/mL): Q: (n=167) -11.7 vs. R: (n=172) 8.4; p<.001 Final Mean prolactin levels (ng/L) in men and women in Q group (11-15); R 91 (women) and 31 (men) Prolactin: Q: mean change from BL: -25.98 ng/mL (doses < 200 mg/day) to -11.35 ng/mL (doses of > 600 mg/day); R: 9.33 ng/mL (doses of < 2 mg/day) to 36.98 ng/mL (doses of > 6 mg/day). Spontaneous reports of sexual and reproductive AE: R: 4.2% (lactation 2, menorrhagia 1, dysmenorrhea 4, vaginitis 1, abnormal sexual function 1, anorgasmia 1, impotence 3, ejaculatory dysfunction 1 vs. Q: 0.6% (dysmenorrhea 2; p=.002) Weight change: p=NS BMI: p=NS Mean change from BL in random serum glucose (mg/dL): LOCF and Completers: p= NS

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Zhong, 2006 R, DB, MC, flexible-dose non-inferiority study 66 centers in US. Inpatients (minimum of 7 days following randomization) then treated on an outpatient basis	Spontaneously reported EPS: Q: 12.7% vs. R: 21.8%; p=.002 AIMS and SAS total scores: greater improvements with Q than R; p= NS BARS score: Q> R; p<.05 % of pts taking anticholinergic medications on a prn basis: Q 5.6% , R 6.9%	351/ 44 Leading to withdraw: Q:(5.9%) vs. R: (6.9%) Withdrew: Due to AE: Q 19, (5.6%); R 25, (7.5%) somnolence: Q: 2, R: 1 EPS: R= 13 (akathisia 4; dystonia 6; extrapyramidal syndrome 1; movement disorder 2). Q: 1 (tardive dyskinesia)	Mean median doses of quetiapine in responders and completers were 574 mg/day and 626 mg/day; respectively. Mean median dose in pts that withdrew due to lack of efficacy: Q: 429mg/day; R 4.7mg/day.

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Zimbroff, 2007 DB RCT 25 centers in US Inpatient	Men and women, 18–70 years of age, primary diagnosis of schizophrenia or schizoaffective disorder: hospitalized for less than 14 consecutive days prior to screening, scores ≥ 4 (at least moderate severity) on the CGI-S, PANSS total score ≥ 80, and a score ≥ 4 on at least two of the PANSS-positive items assessing delusions, hallucinatory behavior or conceptual disorganization.	4 weeks Ziprasidone 40 mg twice daily on day 1, 60 mg twice daily on day 2, and 80 mg twice daily on days 3–14. days 15–28: 40, 60 or 80 mg twice daily n=125 Aripiprazole 15mg every day on days 1–14. days 15–28: 10, 15 or 30 mg daily. n=128	1 day washout	NR

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of outcome assessment timing of assessment	Age Gender Ethnicity	Other population characteristics	Number Screened/ Eligible/ Enrolled
Zimbroff, 2007 DB RCT 25 centers in US Inpatient	Brief Psychiatric Rating Scale (BPRSd) total (derived from the PANSS), PANSS and CGI-S rating scales screening, baseline, and days 2, 4, 7, 14, 21 and 28 (or early termination). The CDSS scale baseline and day 28 (or early termination).	Mean age Ziprasidone 40.8 yrs Aripiprazole 39.8 yrs % Male Ziprasidone 71 Aripiprazole 63 % White, Black, Asian and other Ziprasidone 34, 56, 2 and 8 Aripiprazole 39, 46, 1 and 14		NR/371 screened/256 randomized

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Zimbroff, 2007 DB RCT 25 centers in US Inpatient	79 (31%) / 3 never took meds/ 253	LS mean change (SE) at 4 weeks Ziprasidone CGI-S -1.12 ((0.09) BPRSd total -13.0 ((1.0) BPRSd core -4.3 (0.3) PANSS total -21.6 (1.7) PANSS-EC -2.9 (0.4) Aripiprazole CGI-S -1.15 (0.09) BPRSd total -15.2 (1.0) BPRSd core -5.2 (0.3) P < 0.05 for significant treatment difference favoring aripiprazole PANSS total -24.6 (1.7) PANSS-EC -3.4)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Zimbroff, 2007 DB RCT 25 centers in US Inpatient	Simpson Angus Scale total score (0.0 for ziprasidone and aripiprazole, P=0.99), or the Barnes Akathisia Scale total score (+0.1 for ziprasidone and – 0.1 for aripiprazole, P=0.50). Ziprasidone showed no mean change (0, SE=0.1) from baseline to endpoint in Abnormal Involuntary Movement Scale total score, whereas a decrease of – 0.4 (SE=0.1)	Simpson Angus Scale total score (0.0 for ziprasidone and aripiprazole, P=0.99), Barnes Akathisia Scale total score (+0.1 for ziprasidone and – 0.1 for aripiprazole, P=0.50). Abnormal Involuntary Movement Scale total score, Ziprasidone showed no mean change (0, SE=0.1) from baseline to endpoint vs. aripiprazole decrease of – 0.4 (SE=0.1) (P=0.04). TEAEs n (%) Ziprasidone vs. Aripiprazole Asthenia 7 (5.6) vs. 3 (2.3) Headache 15 (12.0) vs. 22 (17.2) Pain 6 (4.8) vs. 8 (6.3) Constipation 10 (8.0) vs. 14 (10.9) Diarrhea 5 (4.0) vs. 7 (5.5) Dyspepsia 12 (9.6) vs. 23 (18.0) Nausea 8 (6.4) vs. 20 (15.6) Vomiting 12 (9.6) vs. 10 (7.8) Arthralgia 8 (6.4) vs. 5 (3.9) Agitation 14 (11.2) vs. 12 (9.4) Akathisia 7 (5.6) vs. 9 (7.0) Anxiety 7 (5.6) vs. 7 (5.5) Dizziness 9 (7.2) vs. 3 (2.3) Insomnia 8 (6.4) vs. 9 (7.0) Somnolence 33 (26.4) vs. 17 (13.3) Respiratory tract infection 9 (7.2) vs. 3 (2.3) Vaginitis 1 (2.8) vs. 3 (6.3)

Evidence Table 1. Head-to-head trials in patients with schizophrenia

Author, year study design	Extrapyramidal symptoms	Total withdrawals; withdrawals due to adverse events	Comments
Zimbroff, 2007 DB RCT 25 centers in US Inpatient	Ziprasidone vs. Aripiprazole n (%) Extrapyramidal syndrome 11 (8.8) 7 (5.5)	79 withdrawals 13 due to AEs	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Addington, 2004 RCT, multicenter, double-blind Fair	NR	NR	Yes	Yes	Yes	Yes	Yes
Akerele, 2007 Poor	NR	NR	N-higher mean years of education, mean score on ASI, and # days of cocaine use in past 30 days in Olanzapine group	Yes	NR	Yes	Yes
Alvarez, 2006 Fair	Yes - computer generated	Yes - computerized randomization blocks	No - SS differences in baseline body weight (mean O 73.8 kg [SD 14.0] vs R 80.5 kg [SD 15.6 kg]; p=0.0005) and BMI (mean O 25.9 [SD 4.7] vs R 27.5 [SD 5.1]; p=0.007)	Yes	No - open label trial	No - open label trial	No - open label trial
Andrezina, 2006 Fair	Yes - central call in	Yes - central call in	Yes	Yes	Yes	Yes	Yes
Apiquian, 2003 Poor	Not an RCT; Patients allocated consecutively	NA	Yes	Yes	NR	No ("open trial")	No ("open trial")
AstraZeneca #D1441C00112 RCT, DB Multicenter (43 international sites) Fair	Method NR; baseline characteristics seem evenly distributed	NR	Yes	Yes	Unclear	Stated to be Double Blind	Yes
AstraZeneca #D1441C00132 2007	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Yes but method not described	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Addington, 2004 RCT, multicenter, double-blind Fair	Yes	No loss to follow-up	Unclear. "ITT" defined as "all randomized patients with a baseline and >/= 1 post-baseline evaluation	Fair
Akerele, 2007 Poor	Yes O vs. R % patients completed: 43% vs. 71%	Described as "not interested" in Figure1., but described as " did not present for appointments" in text (p265) 7 vs. 3 -> 50% vs. 21%	Unclear; no info in Methods about analysis plans, raw sample sizes provided in Results, except for with HAM reported as using" last observation for each subject" and df=20-> means n=21, which excluded 7/28 14√3.0 = .21	Poor
Alvarez, 2006 Fair	NR	No	No: 235/250 evaluated for effectiveness; 247/250 evaluated for safety	Fair
Andrezina, 2006 Fair	Yes	No	Yes	Good
Apiquian, 2003 Poor	Yes, no, yes, no	No, No	No, excluded non completers (29%)	Poor (for a CCT as high attrition and only completers analyzed)
AstraZeneca #D1441C00112 RCT, DB Multicenter (43 international sites) Fair	Incomplete - reports only withdrawals due to AE	NR / NR Withdrawals due to AE: Placebo 2.7% Quetiapine 400 mg/day 6.9%; 800 mg/day 9.5%	Stated to be	Fair
AstraZeneca #D1441C00132 2007	Yes	Yes/No	No 573/588 (97.4%) in MITT	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Addington, 2004 RCT, multicenter, double-blind Fair	
Akerele, 2007 Poor	
Alvarez, 2006 Fair	
Andrezina, 2006 Fair	
Apiquian, 2003 Poor	
AstraZeneca #D1441C00112 RCT, DB Multicenter (43 international sites) Fair	
AstraZeneca #D1441C00132 2007	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
AstraZeneca #D1444C00133 RCT, DB Multicenter (40 sites in United States) Fair	Method NR; baseline characteristics seem evenly distributed	NR	Yes	Yes	Unclear	Stated to be Double Blind	Yes
Arango, 2009	NR	No open label	No Olanzapine group: worse PANSS total & general psychopathology scores, >Hispanics	Yes	No	No	No
Atmaca, 2003 Fair	NR	NR	Yes	Yes	NR	Yes	NR
Azorin, 2001 Anand, 1998 Double-blind, Multicenter (France and Canada) Fair	Method not reported	Method not reported	No, Significantly more women and lower baseline BPRS score in the risperidone arm	Yes	Not reported	Yes	Yes
Bai, 2006 Fair	Method not reported	NR	Yes	Yes	Yes-SB study where raters were blinded	No-SB study	No-SB study
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study Fair	Method not reported	Not reported	Diagnosis schizophrenia 79% olanzapine vs 87% placebo; schizoaffective disorder 21% olanzapine vs 13% placebo (p=0.049)	Yes	Yes	Not reported	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
AstraZeneca #D1444C00133 RCT, DB Multicenter (40 sites in United States) Fair	Yes	High; not differential Completion overall 59%; by group: Placebo 54% Quetiapine SR 400mg 65%; 600mg 58%; 800mg 60% Quetiapine IR 800 mg=54%	States "modified ITT": analysis excluded 20 (3.5%) of 564 randomized	Fair
Arango, 2009	Yes	No (14%), no	Unclear. ITT included all randomized, but cases with no data after baseline were "eliminated"	Poor
Atmaca, 2003 Fair	Yes	No (1 in each treatment group)	No: 3 of 56 excluded from analysis	Fair
Azorin, 2001 Anand, 1998 Double-blind, Multicenter (France and Canada) Fair	Yes	No	Yes	Fair
Bai, 2006 Fair	Yes	LTFU- low/ Differential: low (only 1-patient withdrew)	Yes (98% completed); used LOCF	Fair
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study Fair	Attrition yes, adherence yes, crossovers and contamination no.	No	Not clear	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
AstraZeneca #D1444C00133 RCT, DB Multicenter (40 sites in United States) Fair	
Arango, 2009	
Atmaca, 2003 Fair	
Azorin, 2001 Anand, 1998 Double-blind, Multicenter (France and Canada) Fair	
Bai, 2006 Fair	
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia	
Olanzapine Relapse Prevention Study Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Bellack, 2004 Double-blind trial Substudy of unpublished trial Poor	Not reported if randomized	Method not reported	Not reported	Yes	Not reported	Yes	Yes
Bitter, 2004 RCT Multi-center, Hungary & South Africa Fair	Method not reported	stated to be "double blind"	Stated to be, data not reported	Yes	Unclear	Yes	Yes
Bondolfi, 1998 Single-center Double-blind RCT Fair	Method not reported	Method not reported	Similar, but number of months in hospital: clozapine: 12.3, risperidone 24.3	Yes	Not reported	Yes	Yes
Bouchard, 2000 Bouchard, 1998 Fair	Method not reported	Method not reported	Yes	Yes	No	No	No
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient Fair	Method not reported	Method not reported	Some differences, NS: Months previously hospitalized: clozapine 8.8, risperidone 12.5 Length of illness (yrs): clozapine 13.9, risperidone 11.1	Yes	Not reported	Yes	Yes
Breier, 2005 Fair-Poor	1:1 ratio, unclear; stated as double blind	NR	Yes OL slightly older than Zip; (p=0.04)	Yes	NR	NR	NR
Byerly, 2008 Fair	NR	Unclear	Yes	Yes	NR	Blinding unclear	Blinding unclear

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Bellack, 2004 Double-blind trial Substudy of unpublished trial Poor	Not by drug	Overall loss to follow-up very high (47-66%), differences by drug not apparent	No	Poor
Bitter, 2004 RCT Multi-center, Hungary & South Africa Fair	Yes	Overall High: 58% NS difference between groups	Yes, using LOCF	Fair
Bondolfi, 1998 Single-center Double-blind RCT Fair	Yes	No	Yes	Fair
Bouchard, 2000 Bouchard, 1998 Fair	Attrition yes, crossovers yes	No/ no	No	Fair
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient Fair	Not reported	Not reported	Yes	Fair
Breier, 2005 Fair-Poor	Yes	Yes; high and differential OL 40.4% vs. Zip 57.6%	Yes; stated not described	Fair-Poor
Byerly, 2008 Fair	Yes	Completion rate: 75% Lost to follow-up: NR Withdrawals by group: NR	Yes	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Bellack, 2004 Double-blind trial Substudy of unpublished trial Poor	
Bitter, 2004 RCT Multi-center, Hungary & South Africa Fair	
Bondolfi, 1998 Single-center Double-blind RCT Fair	
Bouchard, 2000 Bouchard, 1998 Fair	
Breier, 1999 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient Fair	
Breier, 2005 Fair-Poor	
Byerly, 2008 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Canive, 2006 Poor	Unclear " done by computer"	NR	Unclear; this is a crossover study that did not report comparability of important characteristics at baseline of the first treatment period	Yes	Unclear	Unclear	Unclear
Canuso 2009 (CR010498) Fair	Method not described	NR	Yes	Yes	NR	Stated to be Double Blind	Yes
Canuso 2009 Fair	NR	NR	Yes	Yes	NR stated as double blind	NR stated as double blind	Yes
Castle, 2009	No	No	No. Olanzapine group: lower PANSS-EC scores, fewer patients with high agitation level, more women. Regional differences in distribution according to treatment group	Yes	No	No	No
Chan, 2007 Fair	Unclear	NR	Yes	Yes	Unclear	Yes	Yes
Chin, 2006 Fair	NR	NR	Yes	Yes	NR	No-open	No-open
Chiu, 2006 Fair	NR	NR	Yes	Yes	NR	No-open	No-open
Chrzanowski, 2006	NR	NR	Yes, but more acute - phase relapsers randomized to olanzapine	Yes	Unclear, Open-study	No, Open	No, open

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Canive, 2006 Poor	Yes; only 6/15 (40%) completed study	Unclear; discontinuations due to " noncompliance, failed drug screens, and geographic relocation"	No; precluded 60%	Poor, mostly due to high rate of exclusions of analyses.
Canuso 2009 (CR010498) Fair	Yes	No; No Discontinuation rates (%): Paliperidone higher-dose 21.0% Lower-dose paliperidone 30.3% Placebo 41.1%	Stated to be; analysis excluded 6 (1.9%) of 316 randomized.	Fair
Canuso 2009 Fair	Yes	No 77.5% completed in P extended release, 66.7% in quetiapine, 63.8% placebo	No 5/475 (1%) not included in ITT	Fair
Castle, 2009	Yes	No (1.1%), no	Not reported	Poor
Chan, 2007 Fair	Yes- only 62 (75%) completed	None	Yes	Fair
Chin, 2006 Fair	None-100% completion	None	Yes	Fair
Chiu, 2006 Fair	None - 100% completion	None	Yes	Fair
Chrzanowski, 2006	Yes, No, No, No	None	LOCF for 211/214 = 98%	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Canive, 2006 Poor	
Canuso 2009 (CR010498) Fair	
Canuso 2009 Fair	
Castle, 2009	Prospective, observational, non-interventional design
Chan, 2007 Fair	
Chin, 2006 Fair	
Chiu, 2006 Fair	
Chrzanowski, 2006	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Chue, 2005 Fair	NR	NR	No- lLA risp group had greater number of previous hospitalizations	Yes	NR	Yes	Yes
Chue, 2005, RCT, multicenter, double blind, double dummy Poor	NR	NR	No; oral risperidone group had a "marginally significant" greater number of previous hospitalizations	Yes	Yes	Yes	Yes
Citrome, 2001; Volavka, 2002, 2004b, 2004c; Lindenmayer, 2003, 2004 Fair	NR	NR	Yes	Yes	Yes	Yes	Yes
Conley, 2001 Double-blind, Multicenter Fair	Yes	Yes	Similar, but mean age: olanzapine 38.9 yr (SD 10.5); risperidone 41.0 yr (SD 11.0), p = 0.04	Yes	Yes	Yes	Yes
Conley, 2003 Kelly, 2003 Double-blind, single center, crossover Poor	NR	NR	No	Yes	NR	Yes	Yes
Conley, 2005 Fair	Yes	NR	Yes	Yes	NR	NR	NR

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Chue, 2005 Fair	Yes-completion rate of 82%	Unclear-reasons for discontinuation NR	No-16% excluded	Fair
Chue, 2005, RCT, multicenter, double blind, double dummy Poor	Yes	NR	Unclear; number analyzed NR	Poor
Citrome, 2001; Volavka, 2002, 2004b, 2004c; Lindenmayer, 2003, 2004 Fair	Yes: 42% withdrew	No.	Yes (LOCF)	Fair
Conley, 2001 Double-blind, Multicenter Fair	Yes	No	Yes	Good
Conley, 2003 Kelly, 2003 Double-blind, single center, crossover Poor	Yes; 3 withdrew during olanzapine assigned as first drug (23%)	One publication states 3 withdrew during olanzapine assigned as first drug (23%), other publication states that 6 withdrew during olanzapine phase.	No	Fair
Conley, 2005 Fair	Yes	Yes; high and differential RIS 31% QU 42% FLU 64%	Yes	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Chue, 2005 Fair	
Chue, 2005, RCT, multicenter, double blind, double dummy Poor	
Citrome, 2001; Volavka, 2002, 2004b, 2004c; Lindenmayer, 2003, 2004 Fair	
Conley, 2001 Double-blind, Multicenter Fair	
Conley, 2003 Kelly, 2003 Double-blind, single center, crossover Poor	
Conley, 2005 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Covington, 2000 Poor	Method not reported	Method not reported	Not reported	No	No	Not reported	Not reported
Crespo-Facorro, 2006 Fair	NR	NR	Yes	Yes	No-open	No-open	No-open
Csernansky, 2002 Fair	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported	Yes
Cutler, 2008 Fair	Yes	NR	Yes	Yes	NR	Stated to be Double Blind	Stated to be Double Blind
Cutter, 2006 Fair	NR	NR	Yes	Yes	Yes	Yes	Yes
Daniel, 1996 Crossover design Poor	Method not reported	Method not reported	Yes (crossover study)	Yes	Not reported	Not reported	Not reported

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Covington, 2000 Poor	No	Not reported	Not reported	Poor
Crespo-Facorro, 2006 Fair	Yes;7/172 (4%)	No/no	No; 10/182(5%) excluded	Fair
Csernansky, 2002 Fair	Attrition yes NR Adherence yes NR	No/ no	No: 91.9%	Fair
Cutler, 2008 Fair	Yes	No; 66% completed trial	Yes	Fair
Cutter, 2006 Fair	Yes; only 53% completed	No/no	N NR; efficacy sample included all patients who received ≥ 1 dose of study medication and had ≥ 1 post-baseline visit using LOCF. Note: Concern is that with such a high drop-out rate, there is potential for analysis population to also have excluded a large number of patients; with the N, we can't rule this out.	Fair
Daniel, 1996 Crossover design Poor	Yes	No	No	Poor

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Covington, 2000 Poor	
Crespo-Facorro, 2006 Fair	
Csernansky, 2002 Fair	
Cutler, 2008 Fair	
Cutter, 2006 Fair	
Daniel, 1996 Crossover design Poor	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Davidson, 2007 Fair	NR	NR	Yes	Yes	Yes	Yes	Yes
Deberdt, 2008	Method not reported	Method not reported	No Differences in PANSS total and BMI	Yes	NR Stated as double blind	NR Stated as double blind	NR Stated as double blind
Dollfus, 2005 Poor	Method NR	Method NR	Unclear only provided info regarding age, sex and illness duration	Yes	NR	NR	NR
Emsley, 1999 International multicenter (does not include US) Fair	Method not described (just reports that patients were 'randomly' assigned to tx (study design not explicitly reported)	NR	Yes	Yes	Unclear, reported as DB	Unclear, reported as DB	Unclear, reported as DB
Fleischhacker, 2009 Fair	Yes	NR	Yes	Yes	NR	Stated to be Double Blind	Stated to be Double Blind

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Davidson, 2007 Fair	Yes; completion rate = 59%	No/no	No; exceeded 13/618	Fair
Deberdt, 2008	Yes	Not reported	No Included only those with ≥ 1 post baseline evaluation for a given analysis. Data not provided	Fair
Dollfus, 2005 Poor	NR	NR	Unclear number of pts included in analysis. Endpoint analysis excluded non responders (7%)	Poor
Emsley, 1999 International multicenter (does not include US) Fair	Yes NR NR NR	LTFU was combined with other misc noncompletion factors (total 11% of noncompletion factors for each arm) Differential for total withdrawn: NR but there was a higher differential due to AE (~18%) bw risperidone and haloperidol	Yes (all enrolled patients were included)	Fair
Fleischhacker, 2009 Fair	Yes	No 77.9% completed in Olanzapine group 70.7% completed in Aripiprazole	Yes	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Davidson, 2007 Fair	
Deberdt, 2008	
Dollfus, 2005 Poor	76/160 planned sample size enrolled. Study not adequately powered.
Emsley, 1999 International multicenter (does not include US) Fair	
Fleischhacker, 2009 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Garyfallos, 2003 CCT Poor	NR	NR	Yes	No	No	No	No
Gothelf, 2003	No	No	Differences in gender distribution and duration of illness		No	No	No
Green, 2002 Marder, 2003 Fair	Method not reported	Method not reported		Yes	Yes but method not described	Not reported	Yes but method not described
Hamilton, 1998 Fair	Method not reported	Method not reported	SARS score significantly higher in haloperidol group (p=0.0002)	Yes	Yes but method not described	No	Yes but method not described

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Garyfallos, 2003 CCT Poor	Yes	No	Yes	Poor
Gothelf, 2003	Yes 39/43 (90.6%) completed	No, no	No	Poor
Green, 2002 Marder, 2003 Fair	Attrition yes	Not reported	Yes	Fair
Hamilton, 1998 Fair	Yes	No	Yes	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Garyfallos, 2003 CCT Poor	
Gothelf, 2003	Prospective design
Green, 2002 Marder, 2003 Fair	
Hamilton, 1998 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Harvey, 2003a Harvey, 2002a Harvey, 2002b Harvey, 2002c RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands Fair	Method not reported	Method not reported	Yes	Yes	Not clear - states some outcomes masked, but not which or how.	Yes	Yes
Hatta 2009 Fair	NR	NR	Yes (see comments)	Yes	Yes	No	No
Hatta, 2008	Method not reported	Method not reported	Differences between groups in whether the same antipsychotic was assigned and received	Yes	Yes	No	No
Hertling, 2003 Fair	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported	Yes but method not described
Hirsch, 2002 Fair	Yes	No: Envelope method	Yes	Yes	Yes but method not described	Not reported	Yes but method not described

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Harvey, 2003a Harvey, 2002a Harvey, 2002b Harvey, 2002c RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands Fair	Yes	Overall 38% Not differential	Stated LOCF methods, but numbers reported vary by test applied.	Fair
Hatta 2009 Fair	Yes	No loss to follow-up 75% risperidone, 88% olanzapine, 45% quetiapine, and 52% of aripiprazole completed.	No 78/80 in ITT	Fair
Hatta, 2008	No	No, no	No 2/80 (2.5%) excluded	Fair
Hertling, 2003 Fair	No	Not reported	No	Fair
Hirsch, 2002 Fair	Attrition yes	NR	No	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Harvey, 2003a Harvey, 2002a Harvey, 2002b Harvey, 2002c RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands Fair	
Hatta 2009 Fair	High degree of variance among baseline PANSS scores
Hatta, 2008	
Hertling, 2003 Fair	
Hirsch, 2002 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Huang, 2005 Poor	Method not reported	NR	No, baseline characteristics of patients not reported by drug.	No (few exclusion criteria listed but no explicit inclusion criteria reported)	Unclear (study design not reported)	Unclear (study design not reported)	Unclear (study design not reported)
Ingole, 2009	Method not reported	Method not reported	No, differences in BMI	Yes	No	No	No
InterSePT; Meltzer, 2003 Meltzer, 2002 (AO), Potkin, 2003 Meltzer, 1996 RCT - open label, masked ratings Multi-site - 67 sites, 11 countries (US, Europe, South Africa, South America) Good	Yes	Method not reported	Yes, data on alcohol and drug abuse missing	Yes	Yes, for most outcomes. Blinding for reporting of AE's not clear	No	No
Jerrel, 2002 Open-label RCT with economic analysis Fair	Method not reported	Method not reported	Although randomization stratified, and an adaptive randomization procedure used, SS difference on baseline atypical antipsychotic use present. Four other variables NS	Yes	No	No	No
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland,	Method not reported	Method not reported	Yes	Yes	Yes; method not reported	Yes; method not reported	Yes; method not reported

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Huang, 2005 Poor	NR	LTFU-NR Withdrawal rates NR but 97/126 (77%) completed blood sampling and final assessment of severity	No	Poor
Ingole, 2009	NR	NR	NR	Poor
InterSePT; Meltzer, 2003 Meltzer, 2002 (AO), Potkin, 2003 Meltzer, 1996 RCT - open label, masked ratings Multi-site - 67 sites, 11 countries (US, Europe, South Africa, South America) Good	Yes	Overall high: 39%, but similar in groups	Yes, but method not clearly described	Good for efficacy, Poor for AE
Jerrel, 2002 Open-label RCT with economic analysis Fair	Yes	Overall 69% - entirely due to refusals after randomization Due to adaptive randomization, unclear if differences between groups existed	Yes	Fair
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland,	Yes	No; No	Yes	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Huang, 2005 Poor	Lack of randomization, allocation concealment, blinding along with lack of baseline characteristics or ITT indicate potential for important bias
Ingole, 2009	
InterSePT; Meltzer, 2003 Meltzer, 2002 (AO), Potkin, 2003 Meltzer, 1996 RCT - open label, masked ratings Multi-site - 67 sites, 11 countries (US, Europe, South Africa, South America) Good	
Jerrel, 2002 Open-label RCT with economic analysis Fair	
Jeste, 2003 Jeste, 2002 Jeste, 2001 RCT Multinational (US, Israel, Poland,	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Jones, 1998 Purdon, 2000 David, 1999 Multicenter, Canada Double-blind RCT Fair	Yes	Method not reported	Yes	Yes	Not clear	Not clear (dose adjustments)	Yes
Kahn, 2007 RCT, multi-center, international, double-blind, placebo-controlled Fair	Unclear, "dual-matched placebo used to maintain blinding"	Unclear	Yes; Patients taking medication for insomnia was higher in the placebo compared to the quetiapine groups (at week 1 and end of study)	Yes	NR	NR	Yes
Kahn, 2009	Method not reported	Method not reported	Not reported	Yes	No	No	No
Kane 2009 Fair	NR	NR	Yes	Yes	NR stated as double blind	NR stated as double blind	NR stated as double blind
Kane, 2003 Nasrallah, 2004 Fair	Method not reported	Not reported	Similar, but only report baseline on patients receiving at least 1 injection of risperidone.	Yes	Yes	Not clear	Yes
Kane, 2006 Fair	Method not reported	Method not reported	Yes	Yes	Not reported	Yes but method not described	Yes but method not described

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Jones, 1998 Purdon, 2000 David, 1999 Multicenter, Canada Double-blind RCT Fair	Yes	Overall 57% olanzapine 43% risperidone 67% haloperidol 61%	Yes	Fair
Kahn, 2007 RCT, multi-center, international, double-blind, placebo-controlled Fair	Attrition, yes (approx. 76% completed the study); Adherence for all tx groups except Quetiapine XR; crossovers and contamination, no.	No/No	Yes' Modified intention-to-treat (MITT); see page 834 'statistical analysis' section	Fair
Kahn, 2009	Yes	Yes/Yes	Not reported	Poor
Kane 2009 Fair	Yes	Yes 57% of olanzapine completed 49% of aripiprazole completed	No those with 1 post-baseline measure stated to be included	Fair
Kane, 2003 Nasrallah, 2004 Fair	Attrition and adherence (withdrawals due to) yes, others no.	6% in placebo and 75 mg group vs 2% in 25 mg and 3% in 50 mg group.	No. Efficacy evaluation only in patients with at least one post-baseline assessment.	Fair
Kane, 2006 Fair	Attrition reported yes; high, no	Some/ Not differential CHL 12%; ZIP 11%	Yes	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Jones, 1998 Purdon, 2000 David, 1999 Multicenter, Canada Double-blind RCT Fair	
Kahn, 2007 RCT, multi-center, international, double-blind, placebo-controlled Fair	
Kahn, 2009	
Kane 2009 Fair	High rate of noncompliance, missing compliance data
Kane, 2003 Nasrallah, 2004 Fair	
Kane, 2006 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Kane, 2007 Fair	Method not reported	Method not reported	Unclear; difference in the # with disorganized vs. undifferentiated type schizophrenia	Yes	Unclear; reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind
Kane, 2007 Fair	Yes; per computer generated code and was balanced by using permitted blocks and stratified by site	NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind
Karagianis 2009 Fair	NR	NR	Unclear: 3.6% ODO group schizoaffective vs.18.5% of SOT; 8.31% schizophreniform vs. 3.1%; 32.1% bipolar vs. 21.5%	Yes	NR stated as double blind	NR stated as double blind	Yes
Kasper, 2003 Fair	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported	Yes but method not described
Keefe, 2006 OL v RIS v Poor	1:1:1 ratio, stated as double blind	NR	Y	Y	NR	NR	NR
Keks, 2007 Poor	Yes	Yes	Unclear - only provided for 88% of patients	Yes	Unclear - open study	no- open study	no- open study
Kelly, 2008 Fair	NR	NR	Yes	Yes	NR	Stated to be Double Blind	Stated to be Double Blind

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Kane, 2007 Fair	Attrition-yes	LTFU-NR ~25% total withdrawn Differential: overall low, but there was a 6% difference between aripiprazole and	Yes (98% included in ITT); LOCF	Fair
Kane, 2007 Fair	Yes	LTFU- low ~34% total withdrawn Differential: moderate-high when comparing placebo to active treatments; low-moderate differential when comparing among active treatments	Yes (628/630 included as ITT); ANCOVA with LOCF	Fair
Karagianis 2009 Fair	Yes	No	Yes	Fair
Kasper, 2003 Fair	Attrition yes NR NR NR	No/ extent not reported (maximum 22% in aripiprazole; 26% in haloperidol)	No: 99.1%	Fair
Keefe, 2006 OL v RIS v Poor	Y	Y; high and differential OL 43%* RIS 34 % HAL 28%* *stat sign	Y	Poor; due to attrition & 26% randomized to drug they were on before the study
Keks, 2007 Poor	Yes	None	378/618 = 61% analyzed for short-term efficacy 362/618 = 58% analyzed for long-term efficacy	Poor
Kelly, 2008 Fair	Yes	No 71.8% completed risperidone group 77.2% completed olanzapine group	Unclear	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Kane, 2007 Fair	
Kane, 2007 Fair	Authors mention that a study site was audited and they ran their #s with and without 43 patients--there was no difference
Karagianis 2009 Fair	Allocation imbalance, baseline differences
Kasper, 2003 Fair	
Keefe, 2006 OL v RIS v Poor	
Keks, 2007 Poor	
Kelly, 2008 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Kern, 2006 FDA Study 98213 RCT, multicenter, open label Fair	NR	NR	Small differences, favoring aripiprazole, on age (younger), IQ tests (with exception of NAART scores) and PANSS scores (Total, Positive, Negative)	Yes	Not reported	No	No
Kern, 2006 Poor	NR	NR	Unclear, baseline characteristics only provided for 66% included in analysis	Yes	Unclear- open study	No - open Study	No- Open study
Kinon, 2006a RCT, multi-center, double-blind, parallel Poor	Method not reported	Method not reported	Y; Zip group had > use of antipsychotics at or within 20 days before baseline tests [Zip 82.3% vs. Olan 70.8]; accounted for in analysis.	Yes	NR	NR	NR
Kinon, 2006b MC, R, DBT Fair	Yes; per computer generated code and was balanced by using permitted blocks and stratified by site	Yes; identical med blister packs administered by study site personnel	Yes	No (general inclusion criteria were specified but exclusion criteria were not specified)	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes; all study meds were identical in appearance; med blister packs given
Klieser, 1995; Heinrich, 1994 Double-blind, single center, parallel Fair	NR	NR	Unclear; more males and patients older in clozapine group	Yes	Yes	Yes	Yes
Kluge, 2007 Fair	NR	Unclear	Yes	Yes	NR	Stated to be Double Blind	Stated to be Double Blind
Knegtering, 2004 Open, single center, parallel Poor	NR	NR	Yes	Yes	No	No	No

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Kern, 2006 FDA Study 98213 RCT, multicenter, open label Fair	Not reported	Not reported	Unclear - some reported as LOCF, others not.	Fair (based on poster and published abstract only)
Kern, 2006 Poor	Yes, no, yes, no	N/N	169/255 = 66% analyzed	Poor
Kinon, 2006a RCT, multi-center, double-blind, parallel Poor	Yes	High; differential Higher in the Zip group than Olan group (Zip 70.3 vs. Olan 55.4%, p=0.003).	Yes, using MMRM and LOCF	Poor
Kinon, 2006b MC, R, DBT Fair	Yes	LTFU-low ~45% total withdrawn; larger proportion of subjects in quetiapine arm (32%) discontinued due to psychiatric AE compared to olanzapine arm (12.9%)	Not true ITT though authors report it as ITT; used LOCF	Fair
Klieser, 1995; Heinrich, 1994 Double-blind, single center, parallel Fair	Yes: 28/59 (47.5%) withdrew.	No	Yes for some outcomes, unclear for others	Fair
Kluge, 2007 Fair	Yes	No 86% completed trial	Yes	Fair
Knegtering, 2004 Open, single center, parallel Poor	All 51 patients who were analyzed completed the 6-week study period	No loss to follow-up	Not clear - 51 patients "whose data could be analyzed" are reported on	Poor

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Kern, 2006 FDA Study 98213 RCT, multicenter, open label Fair	
Kern, 2006 Poor	
Kinon, 2006a RCT, multi-center, double-blind, parallel Poor	High number of patients taking anti-depressants concurrently during the study [comparable in the tx groups, 52.8%]
Kinon, 2006b MC, R, DBT Fair	
Klieser, 1995; Heinrich, 1994 Double-blind, single center, parallel Fair	
Kluge, 2007 Fair	
Knegtering, 2004 Open, single center, parallel Poor	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Knegtering, 2006 OL v RIS Fair	unclear; open label, says randomized.	Yes	Yes	Yes	No	No	No
Krakowski, 2006 CLO v OL v HOL Fair	Yes; block randomization scheme	Yes	Yes	Yes	Yes	Yes	Yes
Kramer, 2007 Study was terminated early Fair	Yes; computer generated randomization and stratification scheme	Yes, assigned by an interactive voice-response system	Yes; appears that there may be differences between the arms when looking at prior atypical & typical antipsychotics	Yes	Unclear, reported as DB	Unclear, reported as DB	Unclear, reported as DB
Lauriello, 2008	Method not reported	Method not reported	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes
Lee, 1999 Fair	Method not reported	Method not reported	Yes	Yes	No	No	No
Liberman, 2002 Poor	Method not reported	Method not reported	Yes	Yes	Not reported	Not reported	Not reported
Lieberman, 2003 Green, 2004 Fair	Method not reported	Method not reported	No	Yes	Yes but method not described	Not reported	Yes but method not described
Lieberman, 2003 US and Europe Good	Method NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Knegtering, 2006 OL v RIS Fair	No	NR; says all subjects initially randomized finished 6 weeks of meds, did not measure compliance	No	Fair; short study (6 weeks); 13 of 46 (28%) subjects had missing data
Krakowski, 2006 CLO v OL v HOL Fair	Yes	Yes; moderate CLO 35% OL 30% HAL 44%	Yes	Fair; discontinuation was somewhat high for the Hal group, however the study was executed well; inpatient setting, short duration
Kramer, 2007 Study was terminated early Fair	Yes NR NR NR	LTFU- low ~13.5% (28/207) 'drop-outs' Differential: ~8% difference between those in placebo and paliperidone ER arm (more in paliperidone withdrew due to withdrawal of consent)	Study terminated early. Efficacy analyses based on those who received at least 1-dose of tx and 1-postbaseline assessment	Fair
Lauriello, 2008	Yes 132/404 (32.7%) discontinued	No, no 132/404 (32.7%) discontinued	No 402/404 included in ITT	Fair
Lee, 1999 Fair	Attrition yes	No	No	Fair
Liberman, 2002 Poor	NR	NR	NR	Poor
Lieberman, 2003 Green, 2004 Fair	Attrition yes	Not reported	No	Fair
Lieberman, 2003 US and Europe Good	No/No/No/No	NR	Yes	Good

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Knegtering, 2006 OL v RIS Fair	
Krakowski, 2006 CLO v OL v HOL Fair	
Kramer, 2007 Study was terminated early Fair	
Lauriello, 2008	A very high fair. The 2 patients not included in ITT would not have changed the analysis.
Lee, 1999 Fair	
Liberman, 2002 Poor	
Lieberman, 2003 Green, 2004 Fair	
Lieberman, 2003 US and Europe Good	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Lieberman, 2005 (CATIE Study) Good	Yes	Yes, "done under double blind conditions"	Few minor differences	Yes	Yes	Yes	Yes
Lindenmayer, 1998 Open-label Pragmatic trial Poor	Not randomized-patients assigned to treatment based on their willingness to accept weekly blood drawings.	No	No significant differences in characteristics, N=21 clozapine, 14 risperidone.	Yes	No, "independent", but open label	No	No
Lindenmayer, 2008	Method not reported	Method not reported	Unclear QXR 300 mg group had higher % paranoid, lower % undifferentiated	Yes	Yes but method not described	Yes but method not described	Yes
Luthringer, 2007 Fair	Yes, computer generated	Yes, central call center	N-paliperidone patients younger, only gave baseline characteristics of completers (86%)	Yes	Yes	Yes	Yes
Malla, 2004 Canada Poor	Not randomized	No - authors state allocation was influenced by availability based on state-funded reimbursement	Unclear - data only available for those completing treatment	Yes	No	No	No
Marder, 2007 Good	Yes, computer generated	Yes	Yes	Yes	Yes	Yes	Yes
McCue, 2006 Fair	Yes	Yes	Some; mean age varied by up to 6.7 years across groups	Yes	No	No	No

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Lieberman, 2005 (CATIE Study) Good	Yes (74%)	Yes Yes	Yes	Good
Lindenmayer, 1998 Open-label Pragmatic trial Poor	Yes: 5 clozapine vs 2 risperidone withdrawn (24% vs 14%)	No	No: 32/35 analyzed (2 clozapine, 1 risperidone patient not analyzed)	Poor
Lindenmayer, 2008	Yes	Yes/Yes	No 498/532 (94%) in efficacy analysis	Fair
Luthringer, 2007 Fair	Attrition-14%	No/No	Unclear for PANSS, but assume No, as with sleep outcomes	Fair
Malla, 2004 Canada Poor	Yes/Yes/No/No	NR	No - 32/84 enrolled patients analyzed	Poor
Marder, 2007 Good	Yes, No, No, No	No, No	432/444 = 97% analyzed	Good
McCue, 2006 Fair	Yes	No No	No	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Lieberman, 2005 (CATIE Study) Good	
Lindenmayer, 1998 Open-label Pragmatic trial Poor	
Lindenmayer, 2008	
Luthringer, 2007 Fair	
Malla, 2004 Canada Poor	
Marder, 2007 Good	
McCue, 2006 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
McEvoy, 2007 Fair	NR	NR	Yes	Yes	Yes	Yes	Yes
McEvoy, 2007 Good	NR	NR	Yes	Yes	Yes	Yes	Yes
McQuade, 2004 RCT, multicenter, double-blind Fair	NR	NR	Yes	Yes	NR	Yes	Yes
Meltzer, 2008 Fair	Yes	Unclear	Yes	Yes	NR	Double-dummy	Double-dummy
Moller, 2008 Fair	NR	Unclear	Yes	Yes	NR	Double-dummy	Double-dummy
Naber, 2001 Poor	NR - O vs R described as pseudo-randomized, C assignment not random	NR	No - differences in treatment refractoriness, and gender at baseline	Yes	Not blinded	Not blinded	Not blinded
Naber, 2005 Poor	Unclear; states computer program with no details	NR	Yes, small differences (sign NR)	Yes	NR	NR	NR
Newcomer 2009 Fair	Yes	Yes	Yes	Yes	No	No	No

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
McEvoy, 2007 Fair	Attrition-66%	No/No	LOCF of patients who received >= 1 dose of medication and had >= 1 post baseline measurement	Fair
McEvoy, 2007 Good	Yes, No, No, No	No, No	Efficacy Sample = 410/420 (98%) Safety sample = 415/420 (99%)	Good
McQuade, 2004 RCT, multicenter, double-blind Fair	Yes; 72% early discontinuation	No/No	8 patients excluded from "incidence of weight gain" analysis; 3 because they didn't receive study meds and other 5 because they did not have on-treatment weight measurements	Fair
Meltzer, 2008 Fair	Yes	Yes 73.7% completed in olanzapine group 47.6% completed in clozapine group	Unclear	Fair
Moller, 2008 Fair	Yes	No 92.4% completed study	Yes	Fair
Naber, 2001 Poor	Unclear	Unclear	Unclear	Poor
Naber, 2005 Poor	Yes	Y; high and differential Overall 75% lost to follow-up; Lack of efficacy of tx: OL 12% vs. CLO 26% (sign NR)	Yes	Poor
Newcomer 2009 Fair	Yes	Yes 65% of olanzapine completed 86% of quetiapine completed 77% of risperidone completed	No those randomly assigned who were given study treatment per random assignment were included. 20 in primary and 26 in safety analyses were excluded post-randomization	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
McEvoy, 2007 Fair	
McEvoy, 2007 Good	
McQuade, 2004 RCT, multicenter, double-blind Fair	
Meltzer, 2008 Fair	
Moller, 2008 Fair	
Naber, 2001 Poor	
Naber, 2005 Poor	
Newcomer 2009 Fair	20 in primary and 26 in safety analyses were excluded post-randomization because they were randomized despite meeting exclusion criteria

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Newcomer, 2008 Fair	NR	NR	Yes	Yes	NR	Stated to be Double Blind	Yes
Nicolai-Costa, 2007 Poor	No- reported as 'by allotment'	No-open	Yes	Yes	No-open; but those who interviewed and collected data for the DGSFi were blinded to the treatment	No-open	No-open
Perez-Iglesias 2007 Fair	Yes	NR	Mostly, except for haloperidol group has significantly more users of anticholinergics than either the olanzapine or risperidone groups	Yes	Unclear	Stated to be Double Blind	Stated to be Double Blind
Peuskens 2007 Fair	Method not reported	Method not reported	Yes, some differences, with the placebo group being younger (4 years mean), shorter disease duration (0.8 years, mean), and fewer schizophrenic episodes (mean 1.1 fewer).	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Newcomer, 2008 Fair	Yes	No: loss to follow-up 7% in both groups	Unclear	Fair
Nicolai-Costa, 2007 Poor	Attrition-yes (~14%); No patient changed their allocated group	LTFU-low (1-patient) 14% total withdrawn Differential: NR	NR	Poor
Perez-Iglesias 2007 Fair	Yes	No: 88% completed study 2 lost to follow-up in haloperidol group 1 lost to follow-up in olanzapine group 5 lost to follow-up in risperidone group	Stated they analyzed using an ITT analysis, but give explanation for why they present only the per-protocol analysis	Fair
Peuskens 2007 Fair	Yes	Yes/No. Withdrawal rate was 67% compared to 17% in treatment group.	Yes	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Newcomer, 2008 Fair	
Nicolai-Costa, 2007 Poor	
Perez-Iglesias 2007 Fair	
Peuskens 2007 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Peuskens, 1999 Fair	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported	Yes
Potkin, 2003 Fair	NR	NR	Yes	Yes	NR	Yes	Yes
Potkin, 2006 Good	NR	Yes - centralized interactive voice response system (IVRS)	Yes	Yes	Yes	Yes	Yes
Potkin, 2007 Fair	NR	NR	Yes	Yes	NR	Stated to be Double Blind	Yes
QUEST; Mullen, 2001 Mullen, 1999 Reinstein, 1999 Fair	Method not reported	Method not reported	Yes	Yes	No	No	No

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Peuskens, 1999 Fair	Attrition yes	No/ no	No	Fair
Potkin, 2003 Fair	Yes	Unable to determine, groups not reported.	No: 392/404 analyzed	Fair
Potkin, 2006 Good	Yes - 51/382 (13%)	Higher in placebo group (15%) compared to risperidone (3%) and quetiapine (6%)	no-excluded 3 patients (0.8%)	Good
Potkin, 2007 Fair	Yes	Yes: 34% completed in placebo group, 46% completed in asenapine group, 42% completed in risperidone group	Unclear: 8 patients not included in analysis	Fair
QUEST; Mullen, 2001 Mullen, 1999 Reinstein, 1999 Fair	No	NR	Yes, using LOCF	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Peuskens, 1999 Fair	
Potkin, 2003 Fair	
Potkin, 2006 Good	
Potkin, 2007 Fair	
QUEST; Mullen, 2001 Mullen, 1999 Reinstein, 1999 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Riedel, 2005 Fair	Method NR	Method NR	No Higher PANSS Negative SANS alogia SANS avolition-apathy and SANS Total in quetiapine group (page 434)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes
Ritchie, 2003, 2000 Pragmatic RCT Multicenter, Australia Fair	Yes	Yes	Small differences in mean baseline doses of typical antipsychotics, baseline rate of TD and # in residential care	Yes	No	No	No
Robinson, 2006 Fair	NR	NR	Yes	Yes	Yes	No	No
Rosenheck, 1997 Fair	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported	Yes
Rosenheck, 2003 Fair	Method not reported	Yes	Yes, except mean PANSS negative subscale 23.2 in olanzapine vs 21.7 in haloperidol (p=0.02)	Yes	Yes but method not described	Not reported	Yes
Rubio, 2006 Poor	No-allocated alternately	No	Yes	Yes	Yes	No	No
Sacchetti, 2008 Fair	Yes	Unclear	Pretty much: Risperidone group slightly older than olanzapine and quetiapine groups	Yes	Yes	No	Yes
Sacchetti, 2009 Fair	Method not reported	Method not reported	Differences in DAI-10 scores, historical causes of refractoriness	Yes	NR stated as double blind	NR stated as double blind	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Riedel, 2005 Fair	Yes	No: loss to follow-up: Q 2/22 (9%) v R 0	Efficacy analysis based on pts w/baseline and at least one postbaseline measurement w/LOCF; all pts included in safety analysis	Fair
Ritchie, 2003, 2000 Pragmatic RCT Multicenter, Australia Fair	Yes	No	Stated to use LOCF, but 5 risperidone patients not included	Fair
Robinson, 2006 Fair	Yes, No, No, No	None	Analysis excluded 8 (7%) of patients due to protocol violations or refusal of treatment	Fair
Rosenheck, 1997 Fair	Attrition yes; crossovers yes	No/ no	No	Fair
Rosenheck, 2003 Fair	Attrition yes	No/ no	Yes	Fair
Rubio, 2006 Poor	Yes 4/66	No/No	N-4/66 excluded	Poor
Sacchetti, 2008 Fair	Yes	No; No	Yes	Fair
Sacchetti, 2009 Fair	Yes 90/147 completed (61.2%)	No/ no 90/147 completed (61.2%)	No All randomized with $\geq$ 1 dose + baseline measure + $\geq$ 1 valid post-baseline PANSS	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Riedel, 2005 Fair	
Ritchie, 2003, 2000 Pragmatic RCT Multicenter, Australia Fair	
Robinson, 2006 Fair	
Rosenheck, 1997 Fair	
Rosenheck, 2003 Fair	
Rubio, 2006 Poor	
Sacchetti, 2008 Fair	
Sacchetti, 2009 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Saddichha 2008 Fair	NR	NR	Risperidone vs olanzapine: Lower baseline HDL (33.8 vs 40.0). Age comparison NR. Similar for gender and weight and glucose parameters.	Yes	Yes	Yes	Yes
Sayers, 2005 Fair-Poor	Method not reported	Yes	Unclear; only age, smoking and cocaine use given	Yes	Yes	Not reported	Yes
Schering-Plough #7501012 RCT, DB Multicenter (Croatia, India, Latvia, Russia, United States) Fair	Unclear	NR	NR for DB phase between groups (asenapine v. placebo)	Yes	Unclear	Stated to be Double Blind	Stated to be Double Blind
Schering-Plough #041023 RCT, DB Multicenter (USA, Canada, India, Russia, Romania) Fair	Yes	NR	Yes, except fewer females on asenapine	Yes	Unclear	Yes	Yes
Schering-Plough Study 25544	Unclear Interactive voice response system	Unclear Interactive voice response system	Unclear; inadequate data provided	Yes	Unclear; reported as double blind	Unclear; reported as double blind	Yes
Schering-Plough Study 25543	Unclear Interactive voice response system	Unclear Interactive voice response system	Unclear; inadequate data provided	Yes	Unclear; reported as double blind	Unclear; reported as double blind	Yes
Schering-Plough Study 25517	Unclear Central interactive voice response system	Unclear Central interactive voice response system	Unclear; inadequate data provided	Yes	Unclear; reported as double blind	Unclear; reported as double blind	Yes
Schering-Plough Study 041022	Unclear Central interactive voice response system	Unclear Central interactive voice response system	Unclear; inadequate data provided	Yes	Unclear; reported as double blind	Unclear; reported as double blind	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Saddichha 2008 Fair	Yes	Dropouts not reported by group 90% completed study	No, excluded non completers (10%)	Fair
Sayers, 2005 Fair-Poor	Attrition yes	High/Not differential 42% in each group	Yes	Fair-Poor Rating, small study, demographics not provided; high drop out but unclear #'s
Schering-Plough #7501012 RCT, DB Multicenter (Croatia, India, Latvia, Russia, United States) Fair	Yes	High; differential NR. Overall completion, DB phase: 37.5% Attrition NR between groups (asenapine v. placebo)	Stated to be; analysis excluded 1 of 192 randomized	Poor
Schering-Plough #041023 RCT, DB Multicenter (USA, Canada, India, Russia, Romania) Fair	Yes	High; not differential Completion rates: Asenapine 5 mg = 63%; 10 mg = 67% Placebo = 57% Haloperidol 4 mg = 59%	Stated to be; Analysis excluded 10 (2%)of 458 randomized	Fair
Schering-Plough Study 25544	Yes	No/No	No 279/306 (91%) in ITT	Fair
Schering-Plough Study 25543	Yes	Yes/Yes 35% vs. 20% withdrawals	No 433/481(90%) in ITT	Fair
Schering-Plough Study 25517	Yes	Yes/Yes 62% vs. 43% withdrawals	No 1166/1225 (95%) in ITT	Fair
Schering-Plough Study 041022	Yes	No/Yes 53% vs. 48% vs. 53% withdrawals	No 259/277 (94%) in ITT	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Saddichha 2008 Fair	
Sayers, 2005 Fair-Poor	
Schering-Plough #7501012 RCT, DB Multicenter (Croatia, India, Latvia, Russia, United States) Fair	
Schering-Plough #041023 RCT, DB Multicenter (USA, Canada, India, Russia, Romania) Fair	
Schering-Plough Study 25544	
Schering-Plough Study 25543	
Schering-Plough Study 25517	
Schering-Plough Study 041022	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Schering-Plough Study 041021	Unclear Central interactive voice response system	Unclear Central interactive voice response system	Unclear; inadequate data provided	Yes	Unclear; reported as double blind	Unclear; reported as double blind	Yes
Schooler, 2005 Fair	Method NR	Method NR	Yes	Yes	Unclear; reported as double blind	Unclear; reported as double blind	Unclear; reported as double blind
Sechter, 2002 Fair	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported	Yes but method not described
Shopsin, 1979 Fair	Method not reported	Method not reported	Not reported	Yes	Yes	Yes	Yes
Shrivastava, 2000 Poor	Method not reported	Method not reported	Unclear	No	No	No	No
Silva de Lima, 2005 Fair	Performed centrally	Investigators received sealed, numbered ,coded envelopes from a person who had no contact w/the persons evaluation.	Yes	Yes	Yes-blinded to allocation, no contact with doctors or patients' records	No-open	No-open
Simpson, 2004 Fair	NR	NR	69% olanzapine vs 62% ziprasidone male (NS); otherwise similar	Yes	NR (states double-blind, but no details)	Used masked blister packs, and included "A, B, or C" corresponding to low, medium, or high dose.	Used masked blister packs, and included "A, B, or C" corresponding to low, medium, or high dose.
Sirota, 2006 Fair	Method NR	Method NR	Yes, although quetiapine points had a slightly longer duration of illness (15.9 yrs [SD 9.1] vs 13.3 yrs [SD 7.4] for olanzapine)	Yes	Unclear, stated as "rater-blinded"	Unclear, stated as "rater-blinded"	NR
Smelson, 2006 Fair	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Schering-Plough Study 041021	Yes	No/Yes 42.3% vs. 50% vs. 50% vs. 43.1% withdrawals	No 386/417 (93%) in ITT	Fair
Schooler, 2005 Fair	Yes (36.5%), no, no, no	Overall withdrawals 36.5%; p=0.40 between groups	Yes	Fair
Sechter, 2002 Fair	Attrition yes	No/ no	No	Fair
Shopsin, 1979 Fair	Unclear	Differential loss to f/u in placebo group	No	Fair
Shrivastava, 2000 Poor	Yes	NR/No (33%)	No	Poor
Silva de Lima, 2005 Fair	Yes-13%	No/no	Unclear-provided results for 'completers' and 'LOCF', but did not provide any sample sizes; presume LOCF is ITT	Fair
Simpson, 2004 Fair	Yes	High- 37/136 (27.2%) ziprasidone, 25/133 (18.8%) olanzapine (p=0.10)	Yes	Fair
Sirota, 2006 Fair	Yes	No loss to follow-up (all 5 withdrawals accounted for)	Unclear # analyzed NR	Fair
Smelson, 2006 Fair	Yes - 12/31 (39%) dropped out	Unclear- Reasons for drop-outs NR	No- Excluded 39% (completers only)	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Schering-Plough Study 041021	
Schooler, 2005 Fair	
Sechter, 2002 Fair	
Shopsin, 1979 Fair	
Shrivastava, 2000 Poor	
Silva de Lima, 2005 Fair	
Simpson, 2004 Fair	
Sirota, 2006 Fair	
Smelson, 2006 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Smith, 2009	Yes	Method not reported	Differences in type and number of antipsychotics used. Not statistically significant. Analysis adjustment used to control for bias.	Yes	No	No	No
Suzuki, 2007 Poor	NR	NR	Yes	Yes	Open label	Open label	Open label
Tollefson, 1997 Breier, 1999 Gilmore, 2002 Goldstein, 2002 Gomez, 2001 Hamilton, 2000 Kennedy, 2003 Kinon, 2001 Revicki, 1999 Sanger, 1999 Tohen, 2001 Tollefson, 1998 Tollefson, 1999 Tran, 1999 Tunis, 1999 Fair	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported	Yes but method not described
Tollefson, 2001 Beasley, 1999 Beuzen, 1998 Fair	Method not reported	Method not reported	Some differences. Proportion with disorganized type Schizophrenia 23% in O group, 14% in C, while undifferentiated = 13% in O, 24% in C. Also, those with continuous course = 54% in O, 48% in C. Mean age, and other important characteristics not reported per group.	Yes	Yes	Yes	Yes
Tran, 1997 Fair	Method not reported	Method not reported	Unclear - not well reported	Yes	NR	Yes	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Smith, 2009	Yes 44/49 (89.8%) completed	No; no	No 46/49 (93.9%) in ITT	Fair
Suzuki, 2007 Poor	Yes	No; No	No	Poor
Tollefson, 1997 Breier, 1999 Gilmore, 2002 Goldstein, 2002 Gomez, 2001 Hamilton, 2000 Kennedy, 2003 Kinon, 2001 Revicki, 1999 Sanger, 1999 Tohen, 2001 Tollefson, 1998 Tollefson, 1999 Tran, 1999 Tunis, 1999 Fair	Attrition yes	No/ no	No	Fair
Tollefson, 2001 Beasley, 1999 Beuzen, 1998 Fair	Yes	No	Yes (LOCF methods)	Fair
Tran, 1997 Fair	Yes	Overall 47.5% olanzapine 57.6% risperidone 47.3%	Yes	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Smith, 2009	Random assignment, open label
Suzuki, 2007 Poor	
Tollefson, 1997 Breier, 1999 Gilmore, 2002 Goldstein, 2002 Gomez, 2001 Hamilton, 2000 Kennedy, 2003 Kinon, 2001 Revicki, 1999 Sanger, 1999 Tohen, 2001 Tollefson, 1998 Tollefson, 1999 Tran, 1999 Tunis, 1999 Fair	
Tollefson, 2001 Beasley, 1999 Beuzen, 1998 Fair	
Tran, 1997 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Tran-Johnson, 2007 Fair	Method not reported	Method not reported	Yes	Yes	NR	Stated to be Double Blind	Stated to be Double Blind
Tschoner, 2009 Poor	NR	NR	Yes	Yes	NR	NR	NR
Tunis 2006 Fair	Method not reported	Method not reported	Yes	Yes	No	No	No
Tzimos, 2008	Method not reported	Method not reported	18% of Paliperidone group over age 75 vs. 5% of placebo group	Yes	Stated to be Double Blind	Stated to be Double Blind	Stated to be Double Blind
van Bruggen, 2003 Poor	NR	NR	Yes (but appears baseline characteristics exclude 2 patients not analyzed). Groups imbalanced: 18 randomized to O, 26 to R.	Yes	Not clear (states "independent")	NR	NR
van Nimwegen, 2008 Fair	NR	Unclear	NR	Yes	Unclear	Stated to be Double Blind	Stated to be Double Blind
Vanelle, 2006 Good	Yes - Computer generated	Yes - Kept by Sanofi-Synthelabo	Yes	Yes	Yes	Yes	Yes
Velligan, 2003 Fair	Method not reported	Method not reported	Yes	Yes	Yes	No	No
Voruganti, 2007 Fair	NR	NR	Yes	Yes	Yes	NR	NR

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Tran-Johnson, 2007 Fair	Yes	No/no	Yes (LOCF)	Fair
Tschoner, 2009 Poor	Implied that all completed the study	Unclear	NR	Poor
Tunis 2006 Fair	Yes	No/No	Yes	Fair
Tzimos, 2008	Yes 79% completed double blind phase	No, yes(84%) of drug group completed 26/38 (68%) of placebo group completed	No included those who had baseline +≥ 1 postbaseline efficacy assessment	Poor
van Bruggen, 2003 Poor	NR	Yes- 2/26 risperidone vs 0/18 olanzapine not included in analysis	No: 2 risperidone patients excluded	Poor
van Nimwegen, 2008 Fair	Yes	No; No	Excluded 3 patients from analysis because they had no postrandomization observable scores	Fair
Vanelle, 2006 Good	Yes - 14/85 early discontinuation	No/No	No - Excluded 2/85 (0.02%)	Good
Velligan, 2003 Fair	Attrition yes	No/ no	No	Fair
Voruganti, 2007 Fair	Yes- 1/86 early discontinuation	No/No	No - 1/86 (1%) excluded	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Tran-Johnson, 2007 Fair	
Tschoner, 2009 Poor	
Tunis 2006 Fair	
Tzimos, 2008	
van Bruggen, 2003 Poor	
van Nimwegen, 2008 Fair	
Vanelle, 2006 Good	
Velligan, 2003 Fair	
Voruganti, 2007 Fair	

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Wahlbeck, 2000 Open-label RCT Fair	Yes	Method not reported	No, Significantly more women in the risperidone arm	Yes	No, open-label	No, open-label	No, open-label
Wang, 2006 RCT, double-blind Fair	Unclear; pharmacists maintained "'randomization schedules", no details provided	Unclear	Yes	Yes	NR	NR	Yes
Weiden, 2009	Method not reported	Method not reported	Not reported	Yes	Adherence attitude assessor blinded	No	No
Wu, 2006 Fair	NR	NR	Yes	Yes	No	NR	NR
Yamashita, 2004 Mori, 2004 RCT, single center, blinding unclear Fair	NR	NR	No	Yes	NR	Blinding unclear	Blinding unclear
Zhong, 2006 Fair	Not stated	Unclear	Yes	Yes	NR	NR	Yes
Zimbroff, 2007 Fair	Yes	Yes	Yes	Yes	Unclear	Stated to be Double Blind	Yes

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Attrition?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Quality rating
Wahlbeck, 2000 Open-label RCT Fair	Yes	Overall = 35% Differential drop-out: clozapine 50%, risperidone 11%	Yes	Fair
Wang, 2006 RCT, double-blind Fair	Yes	Yes; 42% (8) Risp vs. 29% (5) Olan [study states these were similar, no statistics reported]	Yes, using LOCF	Fair
Weiden, 2009	Unclear 19/26 (73%) in RLAT accepted random assignment	Unclear	Yes	Poor
Wu, 2006 Fair	Yes; 8 of 120	No/no	NR	Fair
Yamashita, 2004 Mori, 2004 RCT, single center, blinding unclear Fair	Yes	No loss to follow-up	Unclear if analysis included 2 patients (2.2%) who discontinued early	Fair
Zhong, 2006 Fair	Yes	Yes; high, not differential Completion rates: approx 48% Lost to follow-up; QU v RIS, 7.4 vs 11.9; RIS higher withdrawal due to AE compared to QU	Y	Fair
Zimbroff, 2007 Fair	Yes	No; 68% completed in ziprasidone group 69.5% completed in aripiprazole group	Stated to be, but 6 patients excluded from analysis	Fair

Evidence Table 2. Quality assessment of trials in patients with schizophrenia

Author, year quality rating	Comments
Wahlbeck, 2000 Open-label RCT Fair	
Wang, 2006 RCT, double-blind Fair	Small number of patients.
Weiden, 2009	Prospective randomized controlled design
Wu, 2006 Fair	Physiologic measures only, no data on psychiatric improvement; investigators not blinded to treatment; only 8 weeks long.
Yamashita, 2004 Mori, 2004 RCT, single center, blinding unclear Fair	
Zhong, 2006 Fair	
Zimbroff, 2007 Fair	

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study	42	6 months	Open-label, randomization NR Setting: in-patient and outpatient services of the National Institute of Psychiatry (NIP) in Mexico City.	between 18 and 45 yr old and met DSM-IV criteria for schizophrenia, schizoaffective or provisional schizophreniform disorders; if they they were on their first psychiatric admission due to psychosis (with a maximum duration of illness of 5 yr) and had a baseline Positive and Negative Syndrome Scale (PANSS) positive syndrome score greater than 17 points with two items scoring at least 4 Exclusion- had received treatment for a period longer than 1 month with an equivalent dose of 5 mg/d haloperidol, if they had concomitant medical or neurological illness, current substance abuse or a history of substance dependence, history of bipolar disorder; high risk for suicide or were agitated.	risperidone (1 mg/d), olanzapine (5 mg/d) or haloperidol (1 mg/d).
Crespo-Facorro, 2006 Crespo-Facorro, 2009 Spain	172	6 weeks	Randomized practical clinical trial (acute phase of PAFIP) University hospital clinic	15-60 yrs; met DSM-IV criteria for principal diagnosis of schizophreniform disorder, schizophrenia, schizoaffective disorder, brief reactive psychosis, schizotypal personality disorder or psychosis not otherwise specified; habitually living in the catchment area; no prior treatment with antipsychotic medication or, if previously treated, a total lifetime of adequate antipsychotic treatment < 6 weeks; current psychotic symptoms of moderate severity or greater assessed by 1 of the 5 items on the SAPS; referred to PAFIP Exclusion criteria: DSM-IV diagnosis of mental retardation; met DSM-IV criteria for drug dependence	haloperidol: 3-9 mg/day risperidone: 3-6 mg/day olanzapine: 5-20 mg/day

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study	NR	Biperiden and benzodiazepines	Mean age 25.5 yrs 73.8% male Ethnicity: NR
Crespo-Facorro, 2006 Crespo-Facorro, 2009 Spain	3-5 days (for the 3 patients wo were receiving antipsychotics at first contact)	Lormetazepam and clonazepam permitted for management of agitation, general behavior disturbances, and/or insomnia; if clinically significant EPS occurred, anticholinergic medication (biperiden at dose of up to 8 mg/day) was allowed; antidepressants (sertraline) and mood stabilizers (lithium) permitted if clinically needed	Mean age: 27.3 yrs Male: 62.2% 100% Spanish

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study	Schizophrenia (61.9% n=26), schizoaffective disorder (16.7%, n=7) and schizophreniform disorder, provisional (21.4%)	NR/NR/36	12/NR/30
Crespo-Facorro, 2006 Crespo-Facorro, 2009 Spain	No previous antipsychotic treatment: 98.3% Inpatient: 63.4%	202/182/182	10 withdrawn after randomization 172 analyzed

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Outcome scales	Method of outcome assessment and timing of assessment
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study	PANSS, CDSS, BAS, AIMS	PANSS; CDSS,;AIMS; Barnes akathisia scale at baseline, 3 months and 6 months
Crespo-Facorro, 2006 Crespo-Facorro, 2009 Spain	BPRS, SANS; SAPS; CGI-S; HAM-D; Calgary Depression Scale (CDS); YMRS; Scale of the Udvalg for Kliniske Undersogelser (UKU); Simpson-Angus Scale; AIMS; Barnes Akathisia Scale (BAS)	BPRS, SANS; SAPS; CGI-S; HAM-D; Calgary Depression Scale (CDS); YMRS Adverse Events: Scale of the Udvalg for Kliniske Undersogelser (UKU) EPS: Simpson-Angus Scale; AIMS; Barnes Akathisia Scale (BAS) BPRS, SAPS, SANS, CGI-S and measurements of side effects: baseline, weekly during first 4 weeks, and 6 week study endpoint Affective symptoms measured at baseline and 6-week study endpoint

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Results
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study	Mean scores at endpoint Haloperidol vs. Risperidone vs. Olanzapine Total 38 vs. 65.7 vs. 38.5 Positive 7.4 vs. 13.3 vs. 8.4 Negative 11.5 vs. 17.3 vs. 10.8 CDSS 1.6 vs. 4.3 vs. 0.4
Crespo-Facorro, 2006 Crespo-Facorro, 2009 Spain	Mean change (SD) from baseline to endpoint (haloperidol vs. olanzapine vs. risperidone) CGI-S: -2.5 (1.0) vs. -2.2 (1.1) vs. -2.2 (1.0); P=0.266 BPRS: -25.3 (14.1) vs. -24.5 (14.9) vs. -21.6 (12.0); P=0.308 SANS: -1.1 (6.5) vs. -3.5 (6.0) vs. -2.1 (5.3); P=0.137 SAPS: -9.7 (4.9) vs. -9.0 (4.8) vs. -9.6 (4.3); P=0.679 HAM-D: -5.5 (8.4) vs. -8.3 (6.8) vs. -5.8 (7.5); P=0.132 CDS: -0.1 (3.6) vs. -1.2 (3.3) vs. -0.7 (3.0); P=.256 YMRS: -6.4 (4.5) vs. -6.6 (4.9) vs. -5.9 (4.8); P=0.720 <u>Clinical response rate (>/= 40% BPRS total improvement from baseline:</u> haloperidol: 57.1% risperidone: 52.5% olanzapine: 63.6% <u>Mean time to response (SD):</u> haloperidol: 4.32 weeks (0.24) risperidone: 4.85 weeks (0.21) olanzapine: 4.36 weeks (0.23) Cognitive changes at one year follow-up for 69 patients olanzapine vs risperidone mean (SD)change in SAPS score: -10.70(5.36) vs -11.33(5.01) mean (SD) change in SANS score: -3.50(8.22) vs -2.41 (7.94) mean (SD) change in CDSS:-0.70(3.55) vs -0.70(3.55) vs -0.59 (2.88)

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Adverse events	EPS	Comments
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study	NR	Haloperidol vs. Risperidone vs. Olanzapine mean BAS 0 vs. 0.6 vs. 0.4 mean AIMS 0.3 vs. 0 vs. 0.1	Completers analysis, only
Crespo-Facorro, 2006 Crespo-Facorro, 2009 Spain	Mean change (SD) from baseline to endpoint in EPS severity (haloperidol vs. olanzapine vs. risperidone) BAS: 0.66 (1.16) vs. 0.13 (0.64) vs. 0.36 (0.91); P=0.012 Simpson Angus Scale: 2.27 (2.62) vs. 0.25 (1.61) vs. 1.31 (2.55); P=0.000 Adverse events reported (risperidone vs. olanzapine vs. haloperidol): Concentration difficulties: 14.3% vs. 3.6% vs. 3.3%; P=0.044 Asthenia: 42.9% vs. 29.1% vs. 27.9%; P=0.169 Sleepiness/sedation: 46.4% vs. 45.5% vs. 23.0%; P=0.012 Increased duration of sleep: 23.2% vs. 12.7% vs. 6.6%' P=0.033 Increased salivation: 17.9% vs. 3.6% vs. 14.8%; P=0.055 Reduced salivation: 12.5% vs. 12.7% vs. 4.9%; P=0.270 Weight gain (increase >/=4kg): 8.9% vs. 47.3% vs. 23.0%; P<0.001 Erectile dysfunction: 13.9% vs. 3.0% vs. 7.9%; P=0.244 Ejaculatory dysfunction: 5.6% vs. 0.0% vs. 13.2%; P=0.072 Amenorrhea: 10.0% vs. 0.0% vs. 8.7%' P=0.549	Prescribed anticholinergics for EPS during treatment (haloperidol vs. risperidone vs. olanzapine): 74.5% vs. 32.8% vs. 3.8%; P<0.0001 Rigidity: 14.3% vs. 0.0% vs. 4.9%; P=0.005 Hypokinesia: 19.6% vs. 1.8% vs. 8.2%; P=0.006 Tremor: 7.1% vs. 3.6% vs. 8.2%; P=0.633 Akathisia: 23.2% vs. 5.5% vs. 14.8%; P=0.029	

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Emsley, 1999 Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden	183	6 weeks	Randomized double blind study	15 to 45 years; had a diagnosis of provisional schizophreniform disorder (295.40) or schizophrenia without prior treatment according to DSM-III-R; psychotic symptoms requiring an oral antipsychotic agent; had received a maximum of 3 days of emergency treatment for this disorder; Exclusion- had clinically relevant neurological, electrocardiographic, or laboratory test abnormalities; pregnant or lactating; women of reproductive age not using adequate contraception; mental illness other than schizophreniform disorder or schizophrenia (according to Axis I of DSM-IH-R); psychoactive substance abuse (DSM-III—R criteria)	risperidone or haloperidol 2- 8 mg/day for 6 weeks
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse	262	12 weeks	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
Emsley, 1999 Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden	NR	Antiparkinsonian drugs or benzodiazepines	Median age 24-26 years Male 67% 62% white 17% oriental 15% black 6% other
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Emsley, 1999 Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden	Age at onset of first symptoms of psychosis (median)=23.5 years Primary diagnosis (% patients): Provisional schizophreniform disorder=93.5 Paranoid schizophrenia=4.5 Undifferentiated schizophrenia=1.5 Disorganized schizophrenia=0.5 Level of functioning (% patients): 1-20=11.4 21-50=74.6 51-80=13.9	NR/NR/NR	46/NR/182
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Outcome scales	Method of outcome assessment and timing of assessment
Emsley, 1999 Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden	PANSS, BPRS; Extrapyramidal Symptom Rating Scale	Baseline, weeks 1, 2, 4, 6
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse	Same as Lieberman 2003	Same as Lieberman 2003

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Results
Emsley, 1999 Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden	Clinically improved according to total PANSS scores Risperidone 63% vs. haloperidol 56% (p = 0.19), and Improved according to total BPRS scores Risperidone 65% and haloperidol 55% (p = 0.08) CGI change scale - much or very much improved; Risperidone 71% vs. haloperidol 70%
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse	Within-group (olanzapine or haloperidol) RR (95% CI) of response for non-substance abusers compared to substance abusers: Substance abuse disorder: olanzapine=1.24 (0.98, 1.57), haloperidol=1.01 (0.80, 1.29) Alcohol use disorder: olanzapine=1.47 (1.21, 1.79), haloperidol=1.10 (0.85, 1.42) Cannabis use disorder: olanzapine=1.18 (0.92, 1.50), haloperidol=0.99 (0.76, 1.28) Mean change in PANSS Total Score for substance use vs non-substance use within olanzapine or haloperidol groups (all p-values NS): Substance abuse vs non-substance abuse: olanzapine=17.37 vs 19.77, haloperidol=15.20 vs 18.43 Alcohol abuse vs non-alcohol abuse: olanzapine=15.27 vs 19.73, haloperidol=14.13 vs 18.09 Cannabis use vs non-cannabis use: olanzapine=15.94 vs 20.16, haloperidol=13.44 vs 18.64

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Adverse events	EPS	Comments
Emsley, 1999 Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden	Haloperidol vs. risperidone Total AEs 90% vs. 78% p < 0.05 Insomnia 16% vs. 10% Headache 10% in each group Agitation 11% vs. 8% Anxiety 8% in each group	Antiparkinsonian medications required - haloperidol 75% vs. risperidone 50%; p < 0.001 Shift from baseline Haloperidol vs. risperidone Questionnaire 5.1 vs. 3.9 p = 0.101 Hypokinesia factor 5.4 vs.4.5 p = 0.273 Hyperkinesia factor 2.4 vs. 1.4 p = 0.007 Parkinsonism total 8.1 vs. 6.1 p = 0.060 Parkinsonism + dystonia 8.6 vs. 6.3 p = 0.060 Parkinsonism + dystonia + dyskinesia 9.0 vs. 6.5 p = 0.046 CGI Parkinsonism severity 2.2 vs. 1.9 p = 0.150	
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse	NR	NR	

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Green, 2006 Companion to Lieberman, 2003: Two-year data	263	2 yrs	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003
Kahn, 2009 50 sites in 14 countries data from EUFEST study	498	12 months	Open study, multicenter	first episode schizophrenia patients with minimal prior antipsychotic treatment	haloperidol (1-4 mg/day; n=103), amisulpride (200-800 mg/day; n=104), olanzapine (5-20 mg/day; n=105), quetiapine (200-750 mg/day; n=104), or ziprasidone (40-160 mg/day; n=82) 12 months

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
Green, 2006 Companion to Lieberman, 2003: Two-year data	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003
Kahn, 2009 50 sites in 14 countries data from EUFEST study	NR	NR	NR

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Green, 2006 Companion to Lieberman, 2003: Two-year data	Same as Lieberman 2003	Same as Lieberman 2003	216 (82%) withdrawn/14 (5%) lost to fu (olanzapine=11% vs haloperidol=3%, p=0.0138)/N analyzed unclear (see comment)
Kahn, 2009 50 sites in 14 countries data from EUFEST study	NR	NR/NR/498	243/NR/not clear

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Outcome scales	Method of outcome assessment and timing of assessment
Green, 2006 Companion to Lieberman, 2003: Two-year data	Same as Lieberman 2003	Same as Lieberman 2003
Kahn, 2009 50 sites in 14 countries data from EUFEST study	NR	Treatment discontinuation; (re)hospitalization rates, psychopathology, severity of illness, and measures of safety and tolerability

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Results
Green, 2006 Companion to Lieberman, 2003: Two-year data	**PANSS Total Score:** no differences between olanzapine and haloperidol groups at weeks 12, 24, 52 and 104 (data NR, Figure 1 reflects symptom changes over time based on results of a mixed repeated measure model analysis) **MADRS:** Lower values for olanzapine vs haloperidol at weeks 12 (p<0.008) and 24 (p<0.045), but not at weeks 52 and 104 (data NR) % patients remaining on treatment at 2 years: olanzapine=23.4% vs haloperidol=12.1%, p<0.0161 Mean survival time in treatment (days): olanzapine=322.09 vs haloperidol=230.38, p<0.0085 Response rates (% patients): olanzapine=67.18% vs haloperidol=59.85%, p=NS Remission rates (% patients): olanzapine=57.25% vs haloperidol=43.94%, p<0.036 Time to remission: trend toward shorter time for olanzapine (p=0.12)
Kahn, 2009 50 sites in 14 countries data from EUFEST study	haloperidol vs amisulpride vs olanzapine vs quetiapine vs ziprasidone Treatment discontinuations: 72% vs 40% vs 33% vs 53% vs 45% Comparisons with haloperidol showed lower risks for discontinuation for amisulpride (HR, 0.36; 95% CI, 0.23 to 0.55), olanzapine (HR, 0.27; 95% CI, 0.17 to 0.42), quetiapine (HR, 0.49; 95% CI, 0.33 to 0.73), and ziprasidone (HR, 0.47; 95% CI, 0.29 to 0.76).

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Adverse events	EPS	Comments
Green, 2006 Companion to Lieberman, 2003: Two-year data	Withdrawals due to AE's: olanzapine=7/131 (5%) vs haloperidol=19/132 (14.4%); p=0.0147 (StatsDirect) Weight gain (mean kg): olanzapine=10.2 vs haloperidol=4.0, p-value NR Greater than 7% weight gain (% patients): olanzapine=72% vs haloperidol=42%, p<0.0001 Cholesterol level (mg/dl): olanzapine=140 vs haloperidol=133, p=0.005 Non-fasting glucose level: greater with olanzapine at weeks 12 and 24, but not later (data NR) Fasting blood glucose: similar in both groups (data NR) At least 1 abnormal SGOT: olanzapine=54.2% vs haloperidol=22%, p<0.0001 At least 1 abnormal SGPT: olanzapine=63.4% vs haloperidol=28.8%, p<0.0001 At least 1 abnormal prolactin level: olanzapine=49.6% vs haloperidol=67.4%, p<0.0040 Serum prolactin level at endpoint: no between-group differences (data NR)	Simpson-Angus Scale (max value): olanzapine=4.57 vs haloperidol=2.28, p<0.001 Barnes Scale (max value): olanzapine=2.83 vs haloperidol=0.98, p<0.0001 AIMS: no between-groups difference, data NR Anticholinergic use (% patients): olanzapine=20% vs haloperidol=47%, p<0.0001	It was noted that not all subjects finished all measurements at their final visit before dropping out, so on any given measure there were fewer than 263 with follow-up visits, but no N's were provided for any outcomes.
Kahn, 2009 50 sites in 14 countries data from EUFEST study	NR	NR	data from the European First Epidsode Schizophrenia Trial (EUFEST)

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group	263	12 wk data (planned study up to 104 wks)	RCT Outpatients, inpatients and ER patients Multicenter (14 sites)	Age 16-40 yrs; onset of psychotic symptoms before age 35 yrs; DSM-IV criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder as assessed by using the Structured Clinical Interview for DSM-IV; experienced psychotic symptoms (delusions, hallucinations, thought disorder and grossly bizarre behavior) for 1-60 months; two active psychotic symptoms characterized by at least 2 PANSS psychosis items ≥4 or one psychosis item ≥5; CGI score ≥4; required treatment with antipsychotic drugs on a clinical basis; able to provide informed consent and cooperate with research staff, tests and examinations; use of medically accepted contraception for female patients of childbearing potential	Olanzapine 5-10 mg/day up to wk 6; 5-20 mg/day wk 6-12 Haloperidol 2-6 mg/day up to wk 6; 2-20 mg/day wk 6-12
Malla, 2004 Canada	84	1 yr	CCT	Diagnosis of schizophrenia, schizophreniform psychosis, schizoaffective psychosis or psychosis not otherwise specified; no medial or neurological disorder likely to cause psychotic symptoms; treatment with only one antipsychotic (risperidone or olanzapine) during the first year; no previous exposure to antipsychotics; completion of ratings of positive and negative symptoms, motor side effects and a neurocognitive battery close to the time of initiation of antipsychotic treatment and 1 year later	Risperidone: allowed dose 1-6 mg/day; median dose 2.5 mg/day Olanzapine: allowed dose 5-20 mg/day; median dose 10 mg/day

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group	antipsychotics washout 2-14 days depending on clinical status	Medications for insomnia or agitation (lorazepam, diazepam, chloral hydrate) or antipsychotic side effects (benzatropine, biperiden, propanolol, procyclidine)	Mean age 23.8 yrs (SD 4.8) 82% male 53% Caucasian 38% African descent 3% East/Southeast Asian 0.8% West Asian 5% Hispanic 2% Other (% >100 due to rounding)
Malla, 2004 Canada	NR	Antidepressants (sertraline, paroxetine, venlafaxine, citalopram and nefazodone) and anti-anxiety medications (lorazepam and clonazepam)	Mean age 23.7 yrs (SD 7.4) 63% male Ethnicity NR (note: these characteristics are based on the 32 pts included in the final analysis)

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group	Duration of previous antipsychotic use: 5.9 wks (SD 10.7) Diagnosis: schizophrenia 59% schizoaffective disorder 10% schizophreniform disorder 31%	NR/NR/263	104/NR/263
Malla, 2004 Canada	Mean age at diagnosis: 21.6 yrs	NR/NR/84	52/NR/32

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Outcome scales	Method of outcome assessment and timing of assessment
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group	PANSS; CGI Severity; Montgomery-Asberg Depression Rating Scale	Weekly physician-assessments wks 1-6, biweekly wks 7-12
Malla, 2004 Canada	SANS	baseline, 1 year physician assessments

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Results
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group	PANSS mean change, based on observed cases at 12 wks: Total score: O -20.05 (SD 1.55) v H -14.22 (SD 0.87) Negative scale score: O -2.95 (SD 0.51) v H -1.21 (SD 0.66) Positive scale score: O -7.41 (SD 1.64) v H -7.06 (SD 0.83) General scale score: O -9.85 (SD 1.33) v H -6.24 (SD 0.57) PANSS mean change, based on least squares mean at 12 wks: Total score: O -16.23 (SD 4.51) v H -10.67 (SD 4.52) Negative scale score: O -2.27 (SD 0.45) v H -0.76 (SD 0.43) Positive scale score: O -6.24 (SD 1.22) v H -5.77 (SD 1.22) General scale score: O -7.93 (SD 1.72) v H -4.36 (SD 1.73) PANSS between-group p-values, mixed model analysis v LOCF analysis Total score: p<0.02 v p=0.58 Negative scale score: p<0.04 v p=0.89 Positive scale score: p=0.50 v p=0.76 General scale score: p<0.003 v p=0.25 CGI Severity Score, mean change based on observed cases at 12 wks: O -1.34 (SD 0.22) v H -1.02 (SD 0.23) CGI Severity Score, mean change based on least squares means at 12 wks: O -1.01 (SD 0.57) v -0.73 (SD 0.57) CGI between-group p-values: mixed-model analysis p=0.07; LOCF analysis p=0.46 Montgomery-Asberg Depression Rating Scale Score, mean change based on observed cases at 12 wks: O -2.58 (SD 0.25) v H -1.93 (SD 1.56) Montgomery-Asberg Depression Rating Scale Score, mean change based on least squares means at 12 wks: O -1.63 (SD 2.84) v H 0.92 (SD 2.84) Montgomery-Asberg Depression Rating Scale Score between-group p-values: mixed model analysis p<0.02; LOCF analysis p=0.07
Malla, 2004 Canada	SANS Positive symptom score: O baseline: 33.3 (SD 18.2); 1 yr: 2.2 (SD 2.6) R baseline: 24.7 (SD 6.0); 1 yr: 6.2 (SD 10.3) SANS Negative symptom score: O baseline: 29.3 (SD 17.8); 1 yr: 9.6 (SD 6.9) R baseline: 27.6 (SD 15.8); 1 yr:12.6 (SD 8.3)

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Adverse events	EPS	Comments
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group	Weight change: >7% increase in body weight from baseline: O 76/124 (61.5%) v H 28/124 (22.7%);p<0.001 (percentages taken from text; number of patients calculated based on percentages and n listed in Table 3) Mean increase in BMI: O 2.39 v H 0.88; p<0.001 Time to clinically-significant weight gain of ≥ 7% (weeks): olanzapine=5 vs haloperidol=28; hazard ratio 5.19, p<0.0001	Parkinsonism: O 29/111 (26.1%) v H 63/115 (54.8%); p<0.001 Akathisia: O 14/118 (11.9%) v H 62/121 (51.2%); p<0.001	
Malla, 2004 Canada	NR	No difference between groups reported in text; no further data provided	Of note: the results are only based on those pts who stayed on the drug they were initially assigned to AND who were completers (32/84 pts) Also, in Table 2 it is not clear if the 1 year results represent the SANS score at 1 year or the mean change from baseline

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)
McEvoy, 2006 Patel 2009 USA CAFE: Comparison of Atypicals in First Episode of Psychosis	400	52 weeks	Double blind RCT	16–40 years; DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder; be in the first episode of their psychotic illness and been continuously ill for at least 1 month - 5 years. Patients were excluded if a prior psychotic episode had remitted for 3 months or more or if they had prior antipsychotic drug treatment > 16 cumulative weeks; ≥4 on at least one Positive and Negative Syndrome Scale (PANSS; 17) psychosis item and a score ≥4 (moderately ill) on CGI-S; women of childbearing potential had to be using a medically acceptable form of contraception. Exclusion- did not speak English; had a history of mental retardation; pregnant or nursing; had a serious, unstable medical illness; had a known allergy to one of the study medications; serious risk of suicide; or had participated in an investigational drug trial within 30 days	olanzapine (2.5–20 mg/day) quetiapine (100–800 mg/day) risperidone (0.5–4 mg/day)
Robinson, 2006 (Companion paper to Lieberman 2003, Green 2004, Perkins 2004) USA- NY	112	4 months	Randomized, open label, rater blinded	Current diagnosis of DSMIV schizophrenia, schizophreniform disorder, or schizoaffective disorder; age 16 to 40; < 12 weeks of lifetime antipsychotic medication treatment; current positive symptoms or current negative symptoms; for women, a negative pregnancy test and agreement to use a medically accepted method of birth control Exclusion- meeting DSM-IV criteria for a current substance induced psychotic disorder, psychotic disorder due to a general medical condition, or mental retardation; medical condition/ treatment known to affect the brain; any medical condition requiring treatment with a medication with psychotropic effects; medical contraindications to treatment with olanzapine or risperidone; significant risk of suicidal or homicidal behavior.	olanzapine (2.5–20 mg/day) risperidone (1–6 mg/day).

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
McEvoy, 2006 Patel 2009 USA CAFE: Comparison of Atypicals in First Episode of Psychosis	2 week washout	adjunctive antidepressant or mood stabilizer during the first 8 weeks of treatment was not allowed unless approved by the project medical officer. Anticholinergic medications for acute extrapyramidal side effects were permitted for up to a total of 2 weeks over the course of the trial.	Mean age 24.5 years 73% male 51.3% white 43.0% black 5.8% other
Robinson, 2006 (Companion paper to Lieberman 2003, Green 2004, Perkins 2004) USA- NY	NR	Benztropine for extrapyramidal symptoms and lorazepam or propranolol for akathisia.	Mean age 23.3 years Male 70% "diverse ethnic backgrounds" no specifics reported

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
McEvoy, 2006 Patel 2009 USA CAFE: Comparison of Atypicals in First Episode of Psychosis	Schizophrenia 57.8% Schizophreniform disorder 28.8% Schizoaffective disorder 13.5% Age at onset 23.5 years	NR/NR/400	281/0/400
Robinson, 2006 (Companion paper to Lieberman 2003, Green 2004, Perkins 2004) USA- NY	Onset of psychotic symptoms=slightly over 2 years Antipsychotic medication naïve (% patients)=78% Diagnosis (% patients): Schizophrenia=75% Schizophreniform disorder=17% Schizoaffective disorder=8%	474/120/120	23/8/112

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Outcome scales	Method of outcome assessment and timing of assessment
McEvoy, 2006 Patel 2009 USA CAFE: Comparison of Atypicals in First Episode of Psychosis	PANSS, the CGI, and the Calgary Depression Scale for Schizophrenia; Heinrichs-Carpenter Quality of Life Scale Clinical response was defined as a score ≤3 on all PANSS items and ≤3 on the CGI severity item at any time Primary endpoint was all cause discontinuation	Baseline, at weekly intervals for the first 6 weeks, every other week for the next 6 weeks, and monthly thereafter. All clinical and laboratory assessments were obtained at baseline, week 12, and week 52 or when the patient terminated the study before week 52
Robinson, 2006 (Companion paper to Lieberman 2003, Green 2004, Perkins 2004) USA- NY	Response - Substantial improvement a priori as a rating of mild or better on the SADS-C+PD positive symptom items (severity of delusions, severity of hallucinations, impaired understandability, derailment, illogical thinking, and bizarre behavior) plus a CGI rating of much improved or very much improved; substantial improvement be maintained for two consecutive visits. Parkinsonism was defined as being present if two or more of the Simpson-Angus Rating Scale items were rated 2 or one item was rated 3 or higher. An overall extrapyramidal symptom severity score was calculated as the sum of the Simpson-Angus Rating Scale items.	Baseline and every week for the first 4 weeks, then every 2 weeks

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Results
McEvoy, 2006 Patel 2009 USA CAFE: Comparison of Atypicals in First Episode of Psychosis	Overall discontinuation before 52 weeks 70% of patients; 68.4% olanzapine, 70.9% quetiapine, 71.4% risperidone. At 12 weeks mean change from baseline in the PANSS positive subscale scores showed greater reductions for olanzapine (–5.2) and risperidone (–5.1) than for quetiapine (–4.0; quetiapine versus olanzapine, p=0.017; quetiapine versus risperidone, p=0.031) Trmt response at any point in study olanzapine 64%, quetiapine 58% risperidone 65% Olanzapine vs risperidone vs quetiapine Weight gain at 12 weeks LSM (SE) in pounds 15.6 (1.1) vs 8.6 (1.1) vs 7.9 (1.1) Weight gain ≥7% from baseline: Olanzapine vs risperidone 59.8% vs 32.5%, p<0.001, vs Quetiapine 29.2% (p<0.0001) Changes in total PANSS and weight gain: NS at 12 weeks (p=0.936) Weight gain at 52 weeks in pounds 24.2 (1.9) vs 14.0 (1.9) vs 12.1 (1.8), p<0.001 Weight gain of ≥7% from baseline: Olanzapine vs risperidone: 80% vs 57.6%, p<0.05, vs quetiapine 50.0%, p<0.01 No statistically significant difference between changes in total PANSS score and changes in weight at 52 weeks (p=0.338)
Robinson, 2006 (Companion paper to Lieberman 2003, Green 2004, Perkins 2004) USA- NY	Response rates olanzapine (43.7%, 95% CI=28.8%–58.6%) and risperidone (54.3%, 95% CI=39.9%–68.7%).

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Adverse events	EPS	Comments
McEvoy, 2006 Patel 2009 USA CAFE: Comparison of Atypicals in First Episode of Psychosis	Olanzapine Quetiapine Risperidone (%) Weight gain 51.1 40.3 41.4 Increased sleep hours 33.8 41.8 27.1 Insomnia 38.4 29.1 33.8 Menstrual irregularities 31.3 23.8 47.1 Decreased sex drive 27.8 26.1 27.1 Akinesia 24.1 24.6 27.1 Dry mouth 21.8 34.3 15.8 Akathisia 20.3 18.7 22.6 Decreased sexual arousal 21.8 16.4 18.1 Decreased orgasm 16.5 15.7 18.8 Orthostatic faintness 11.3 19.4 12.8 Constipation 8.3 11.9 13.5 Sialorrhea 5.3 6.0 13.5 Skin rash 7.5 5.2 6.8 Gynecomastia 6.8 2.2 9.8 Urinary hesitancy 5.3 5.2 3.0 Incontinence or nocturia 3.8 3.7 3.0 Galactorrhea 2.3 0.0 2.3	According to article "There were no significant differences across treatment" groups	
Robinson, 2006 (Companion paper to Lieberman 2003, Green 2004, Perkins 2004) USA- NY	Weight gain olanzapine 17.3% (95% CI=14.2%–20.5%) vs. risperidone 11.3% (95% CI=8.4%–14.3%)	Extrapyramidal symptom severity scores risperidone 1.4 (95% CI=1.2–1.6) vs. olanzapine 1.2 (95% CI=1.0–1.4) Parkinsonism risperidone 16.0% (95% CI=5.5%–26.6%) vs olanzapine 8.9% (95% CI=0.3%–17.6%)	

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Schooler, 2005 Multi-national	555	2 yrs	Double blind RCT	16–45 year-old Structured Clinical Interview for DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder < 1 year; no more than two psychiatric hospitalizations for psychosis; <12 weeks of cumulative exposure to antipsychotics and required antipsychotic treatment upon enrollment Exclusions- meeting DSM-IV criteria for another axis I diagnosis, including substance dependence or abuse; needing another nonantipsychotic psychotropic medication at enrollment; having a serious or unstable medical illness.	Risperidone (1 to 8 mg/day) or haloperidol (1 to 8 mg/day)
Strakowski, 2005 (companion to Lieberman 2003, Green 2004, Perkins 2004) US & Europe HGDH Research Group	195	1 yr	Same as Lieberman et al 2003.	Same as Lieberman et al 2003.	Haloperidol 2-6 mg/day Olanzapine 5-20 mg/day with adjustments for both during the first 12 wks of study
Perez-Iglesias, 2007 Spain Goes with Crespo-Facorro 2006	145	12 weeks	Open label and randomized in outpatient and inpatient population at psychiatric hospital	Men and women 15 to 50 years, living in region, experiencing their first episode of psychosis (DSM-IV codes 295, 297, and 298), and never treated with antipsychotic medication.	Haloperidol = 4.2 mg/day, Olanzapine = 12.7 mg/day, Risperidone = 3.6 mg/day for 12 weeks

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
Schooler, 2005 Multi-national	3–7-day drug washout period that was waived for extremely ill patients.	Chloral hydrate, zolpidem, or flurazepam for sleep; and lorazepam for agitation.	Mean age 25 years 70% male 74% White 13% African-American 3% Hispanic 10% Other
Strakowski, 2005 (companion to Lieberman 2003, Green 2004, Perkins 2004) US & Europe HGDH Research Group	Same as Lieberman et al 2003	Same as Lieberman et al 2003	Mean age 25 yrs (SD 5) 80% male 55% White 35% African-American 10% Other
Perez-Iglesias, 2007 Spain Goes with Crespo-Facorro 2006	NR	Lormetazepam and clonazepam permitted for management of agitation, general behavior disturbances, and/or insomnia; if clinically significant EPS occurred, anticholinergic medication (biperiden at dose of up to 8 mg/day) was allowed.	Haloperidol vs. Olanzapine vs. risperidone Age 28.6 yrs vs 28.5 yrs vs 26.9 yrs % male 62.5 vs 61 vs 59.6 Ethnicity 96% white

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Schooler, 2005 Multi-national	DSM-IV diagnosis (% patients): Schizophrenia=48.2 Schizoaffective disorder=7.6 Schizophreniform disorder=44.0 No previous antipsychotic exposure (% patients)=31.0 Age at onset of first episode=24.0 years	NR/NR/559	218/0/528
Strakowski, 2005 (companion to Lieberman 2003, Green 2004, Perkins 2004) US & Europe HGDH Research Group	Diagnosis: 61% schizophrenia 30% schizophreniform 9% schizoaffective PANSS total: 81 (SD 15) PAS total: 0.33 (SD 0.16) Duration of illness: 65 wks (SD 62) Duration of previous antipsychotic use: 6 wks (SD 10) Substance abuse disorder: 8% Hospitalized at index: 57%	NR/NR/195	107/NR/195
Perez-Iglesias, 2007 Spain Goes with Crespo-Facorro 2006	Haloperidol vs. Olanzapine vs. Risperidone % Schizophrenia 70 vs. 53.7 vs. 53.2 Schizophreniform disorder 20 vs. 24.4 vs. 21.3 Weight 68.29 vs. 66.39 vs 65.26 BMI 24.33 vs. 22.92 vs 22.2	193/147/145	17/8/128

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Outcome scales	Method of outcome assessment and timing of assessment
Schooler, 2005 Multi-national	PANSS; CGI Severity; EPS rating scale	Assessments with the Positive and Negative Syndrome Scale, CGI, and Extrapyramidal Symptom Rating Scale weekly during the first 4 weeks of the trial and then every 4 weeks for the next 5 months. Months 6–15, every 2 months and every 3 months thereafter.
Strakowski, 2005 (companion to Lieberman 2003, Green 2004, Perkins 2004) US & Europe HGDH Research Group	SF-36	Planned physician assessments at baseline and at 3 mos, 6 mos and 1 year. Included patients had baseline and at least one additional assessment
Perez-Iglesias, 2007 Spain Goes with Crespo-Facorro 2006	BMI and weight baseline and 12 weeks. Also see Crespo-Facorro 2006	Body weight; body mass index; and 12-hours-fasting morning levels of total cholesterol, tri-glycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, glucose, homeostasis model assessment (HOMA) index, and insulin.

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Results
Schooler, 2005 Multi-national	Risperidone vs. haloperidol change from baseline in PANSS Total -21.0 vs. -20.6 p = 0.49 Positive -6.6 vs. -7.0 p = 0.13 Negative -4.8 vs. -4.2 p = 0.98 CGI change score 2.69 vs. 2.62 p = 0.45
Strakowski, 2005 (companion to Lieberman 2003, Green 2004, Perkins 2004) US & Europe HGDH Research Group	No significant time-to-treatment group effects; significant improvement over time observed for all patients for most SF-36 variables for both interventions No further data on treatment groups provided; all other results combined interventions
Perez-Iglesias, 2007 Spain Goes with Crespo-Facorro 2006	Haloperidol vs. Olanzapine vs. Risperidone Weight gain (kg) 3.83 (4.89) vs. 7.46 (5.11) vs 5.58 (4.48) Haloperidol vs. Olanzapine P = 0.004, all other NS BMI gain 1.36 (1.59) vs. 2.62 (1.78) vs 1.87 (1.47) Haloperidol vs. Olanzapine P = 0.008, all other NS For other results see Crespo-Facorro 2006

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Adverse events	EPS	Comments
Schooler, 2005 Multi-national	Weight gain at endpoint risperidone [N=211]: mean=7.5 kg, haloperidol [N=204]: mean=6.5 kg, p=0.26 Suicide ideation risperidone 7.2% (N=20) and no suicides vs. haloperidol 9.4% (N=26) with three completed suicides p = nr	Risperidone vs. haloperidol Dyskinesia Baseline 1.1% vs 1.4% Emergent 8.3% vs. 13.4% Persistent 1.8% vs. 3.3% Extrapyramidal symptoms Total 3.72 vs 4.72 p = 0.04 Parkinsonism, dystonia 3.28 vs. 4.14 p = 0.05 Dystonia 0.34 vs. 0.35 p = 0.91 Parkinsonism 3.12 vs. 3.97 p = 0.05 Dyskinesia 0.82 vs. 1.11 p = 0.12 Akathisia 0.61 vs. 1.00 p < 0.0001	
Strakowski, 2005 (companion to Lieberman 2003, Green 2004, Perkins 2004) US & Europe HGDH Research Group	NR	NR	
Perez-Iglesias, 2007 Spain Goes with Crespo-Facorro 2006	See Crespo-Facorro 2006	See Crespo-Facorro 2006	Goes with Crespo-Facorro 2006

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)
Saddichha, 2007 India	66	6 weeks	RCT, inpatient, single center	Drug-naïve patients with a DSM-IV diagnosis of first episode schizophrenia.	Haloperidol n=15, 15.6 (2.6) mg Olanzapine n=29 , 17(5) mg Risperidone n=22. 4.5 (1.2) mg 6 weeks
Saddichha, 2008 Saddichha 2008 "Predictors of antipsychotic…" Saddichha 2008 "Diabetes and Schizophrenia-effect of disease or drug.." India	99 (includes the 66 above)	6 weeks	RCT, inpatient, single center	Drug-naïve patients with a DSM-IV diagnosis of first episode schizophrenia.	35 on Olanzapine (16.5 ± 4.6 mg), 33 on Risperidone (4.4 ± 1.2 mg) a 31 on Haloperidol (13.4 ± 3.6 mg). 6 weeks

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
Saddichha, 2007 India	NR	None that would effect weight or metabolism	Age 26.7 yrs % male 47 Ethnicity NR
Saddichha, 2008 Saddichha 2008 "Predictors of antipsychotic…" Saddichha 2008 "Diabetes and Schizophrenia-effect of disease or drug.." India	NR	None that would effect weight or metabolism	Age 26.0 (5.5) yrs % male 52.5%

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Saddichha, 2007 India	Weight 48.3 (10.5) BMI 19.2	NR/NR/NR	NR/NR/66
Saddichha, 2008 Saddichha 2008 "Predictors of antipsychotic…" Saddichha 2008 "Diabetes and Schizophrenia-effect of disease or drug.." India	66 (66.7%) paranoid schizophrenia 33 (33.3%) undifferentiated schizophrenia.	NR/NR/110	11/NR/99

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Outcome scales	Method of outcome assessment and timing of assessment
Saddichha, 2007 India	Prevalence of obesity	WHO definition for Asians and International Diabetes Federation criteria
Saddichha, 2008 Saddichha 2008 "Predictors of antipsychotic…" Saddichha 2008 "Diabetes and Schizophrenia-effect of disease or drug.." India	ATP III A and IDF criteria	The presence of the Metabolic Syndrome was assessed using the ATP III A and IDF criteria

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Results
Saddichha, 2007 India	Olanzapine vs. Risperidone vs. Haloperidol Weight gain (kg) 5.1 vs. 4.1 vs. 2.8 Treatment -emergent obesity WHO 10.3% vs. 9.1% vs. 0 IDF 44.8% vs. 36.4% vs. 0
Saddichha, 2008 Saddichha 2008 "Predictors of antipsychotic…" Saddichha 2008 "Diabetes and Schizophrenia-effect of disease or drug.." India	Olanzapine vs. Risperidone vs. Haloperidol Mets by ATP IIIA 20.0% vs. 9.1% vs. 0% Mets by IDF 25.7% vs. 24.2% vs. 3.2%

Evidence Table 3. Randomized controlled trials in patients with first-episode schizophrenia

Author, year Country Trial Name	Adverse events	EPS	Comments
Saddichha, 2007 India	NR	NR	
Saddichha, 2008 Saddichha 2008 "Predictors of antipsychotic…" Saddichha 2008 "Diabetes and Schizophrenia-effect of disease or drug.." India	% of patients with weight gain>7% above baseline: Olanzapine vs Risperidone: 77.1% vs 63.6%, p<0.001 Mean Weight gain at endpoint : Olanzapine: 5.0, Risperidone: 4.2, p<0.001 Increase in Fasting blood sugar at endpoint (mean (SD)) : Olanzapine 6.6(12.7), Risperidone: 4.3 (12.5), p=0.01 Increase in Post prandial blood sugar at endpoint: Olanzapine: 21.5 (32.2), Risperidone: 21.0 (23.4), p<0.001 Treatment emergent Diabetes: (WHO definition) Olanzapine vs Risperidone: 11.4% vs 9.1% (ADA definition) 2.9% vs 0%	NR	

Evidence Table 4. Systematic reviews of trials in patients with schizophrenia

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Nussbaum 2009	To compare effects of oral paliperidone with any other treatments for people with schizophrenia and schizophrenia-like illnesses.	Cochrane Schizophrenia Group's Specialized Register in November 2008	Participants: Schizophrenia or schizophrenia-like illnesses, no age limit **Interventions:** Paliperidone (oral or intramuscular), alone or as an adjunct **Comparisons:** Placebo, alternative psychotropic agent or other methods of treatment **Outcomes:** Primary=Global state and discontinuation, Secondary=numerous **Study designs:** RCT's	Comparison to: Placebo: N=2567 Olanzapine: N=1692 Risperidone: N=76 Quetiapine: N=314	RCT's N=8

Evidence Table 4. Systematic reviews of trials in patients with schizophrenia

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Adverse events
Nussbaum 2009	Schizophrenia	Comparison to: Placebo: 8 trials Olanzapine: 3 trials Risperidone: 1 trial Quetiapine: 1 trial	Response (relative risk, 95% confidence interval): Paliperidone vs olanzapine: 0.90, 0.73 to 1.13 Paliperidone vs risperidone or quetiapine: NR Suicide attempt: Paliperidone vs olanzapine: RR 0.69, CI 0.21 to 2.30	Paliperidone vs olanzapine Extrapyramidal disorder: RR, 2.99; CI, 1.44 to 6.18 Hyperkinesia: RR, 3.14; CI, 21 1.53 to 6.42 Hypertonia: RR, 9.28; CI, 1.26 to 68.51 Barnes Akathisia scale score=0: RR, 0.90; CI, 0.82 to 0.98 Weight change: WMD -0.88 CI -1.38 to -0.37 Paliperidone vs risperidone Extrapyramidal disorder: RR 1.52 CI 0.44 to 5.29 Hyperkinesia: RR 1.01 CI 0.19 to 5.29) Paliperidone vs quetiapine Increase in weight: WMD -0.70 CI -0.74 to -0.66 Hypertonia: RR 3.19 CI 1.31 to 7.77, NNH13 CI 4 to 86 Tremor: RR 2.60 CI 1.39 to 4.88, NNH 9 CI 4 to 34 Akathisia: RR 1.51 CI 0.70 to 3.26

Evidence Table 4. Systematic reviews of trials in patients with schizophrenia

Author Year	Subgroups	Quality Assessment
Nussbaum 2009	None	**1. Report clear review question, state inclusion and exclusion criteria of primary studies?** Yes **2. Substantial effort to find relevant research?** Yes **3. Adequate assessment of validity of included studies?** Yes, Cochrane Risk of Bias **4. Sufficient detail of individual studies presented?** Yes **5. Primary studies summarized appropriately?** Yes **Overall quality rating=Good**

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
Arato, 2002 Europe Inpatients	294	Randomized, DB, parallel group PCT	Inpatients ≥ 18y with chronic, stable schizophrenia (DSM-III-R) hospitalized ≥ 2 months and had scores of ≤ 5 on the CGI-S.
Bai, 2003 Taiwan Inpatients	49	Randomized, DB PCT	Hospitalized patients aged 18-65 years with severe tardive dyskinesia and BPRS <20 and no record of violent or aggressive behavior within 6 months prior to the study.
Baker, 1996 United States Inpatients	29	RCT, DB placebo-controlled trial Multicenter	Inpatients with a DSM III-R diagnosis of chronic schizophrenia

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
Arato, 2002 Europe Inpatients	Ziprasidone 40 mg/d Ziprasidone 80 mg/d Ziprasidone 160 mg/d placebo 52-week study (no dosage adjustments allowed during the study after the first 2 days)	NR/ 3-day wash out for all pts	Only medications permitted: anticholinergic vs, lorazepam for agitation and temazepam (upper limit=20mg) for insomnia	Mean age: 49.7 years Age range: 20-82 years 73% male Ethnicity: NR
Bai, 2003 Taiwan Inpatients	Risperidone up-titrated to 6 mg/d for last 6 weeks of study placebo 12-weeks	NR/ 4-week washout with all original conventional antipsychotics	Other antipsychotics not allowed; anticholinergics were titrated according to the EPS, and benzodiazepines could be prescribed adjunctively if the patients psychiatric condition was unstable.	Mean age: 50.2 years 66.7% male Ethnicity: NR
Baker, 1996 United States Inpatients	Olanzapine 1 mg (n=11) Olanzapine 10 mg (n=7) Placebo (n=7) 6-week treatment period	NR / 1-week washout period before randomization	NR	Mean age: 36 years 68% male Ethnicity: NR

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
Arato, 2002 Europe Inpatients	Smokers: 68.7%	329/ 294/ 278	179/ NR / 277	PANSS CGI GAF
Bai, 2003 Taiwan Inpatients	Mean baseline BPRS score: 13.4 Mean baseline ESRS-parkinsonian score: 2.7 Mean baseline ESRS-dystonia score: 1.8 Mean baseline AIMS score: 15.9	NR/ NR/ 49	7 / 0 / 42	BPRS
Baker, 1996 United States Inpatients	Mean (SD) Global Severity Ratings at baseline for: Obsession: 0.8 (1.2) Compulsions: 0.8 (0.8) On this scale, 0 = no symptoms; 1 = slight symptoms; 2 = mild symptoms	NR/ NR/ 29	4 / NR / 25	see "methods of outcome assessment..." column

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
Arato, 2002 Europe Inpatients	PANSS and CGI scales completed at baseline, and end of weeks 3, 6, 16. 28, 40, and 52. Global Assessment of Functioning (GAF) administered at baseline and weeks 28 and 52.1
Bai, 2003 Taiwan Inpatients	Baseline and endpoint mental status assessed with BPRS.
Baker, 1996 United States Inpatients	Obsessive and compulsive symptoms identified and rated using a scale derived from the Yale-Brown Obsessive Compulsive Scale supplemented by screening questions from the NIMH Diagnostic Interview Schedule (DIS) and by global severity and global change derived from the CGI-S. Ratings were completed at baseline and endpoint (week 6). Elements analyzed for this report: global severity of obsessions, global severity of compulsions, change during DB treatment in overall severity of obsessions, and change during DB treatment in overall severity of compulsions.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
Arato, 2002 Europe Inpatients	34% of ziprasidone patients relapsed (71/206) Ziprasidone 40mg vs ziprasidone 80mg vs ziprasidone 160mg vs placebo Mean change in scores from baseline: PANSS total score: +2.9 vs +1.9 vs -1.3 vs +15.6 (p<0.01 for all Z vs placebo) PANSS Negative subscale: -1.9 vs -1.0 vs -2.8 vs+ 1.4 (p<0.05 for all Z vs placebo) PANSS Positive subscale: +3.0 vs +1.2 vs +1.8 vs +6.2 (p<0.05 for all Z vs placebo) CGI-S: +0.4 vs +0.2 Vs +0.1 vs +1.0 (p<0.01 for all Z vs placebo) CAF: -4.0 vs -1.0 vs -0.9 vs -10.2 (p<0.01 for all Z vs placebo)
Bai, 2003 Taiwan Inpatients	Risperidone (n=22) vs placebo (n=20) group: % of responders: 68% vs 30%, p=0.029 Mean change in BPRS score at endpoint: +1.5 vs +5.3, p=NS
Baker, 1996 United States Inpatients	Mean (+/-SD) Global severity ratings change between baseline and endpoint for all groups: Obsessions: 0 Compulsions -0.2 Global endpoint ratings of change from baseline in obsessive symptoms : % of patients saying symptoms improved vs unchanged vs worse Olanzapine 1 mg (n=11) : 9.1% vs 63.6% vs 27.3% Olanzapine 10 mg (n=7): 28.6% vs 42.8% vs 28.6% Placebo (n=7): 0% vs 71.4% vs 28.6% Global endpoint ratings of change from baseline in compulsive symptoms : % of patients saying symptoms improved vs unchanged vs worse Olanzapine 1 mg : 9.1% vs 81.8% vs 9.1% Olanzapine 10 mg: 0% vs 85.7% vs 14.3% Placebo:28.6% vs 71.4% vs 0%

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
Arato, 2002 Europe Inpatients	SARS, Barnes Akathisia, and AIMS administered
Bai, 2003 Taiwan Inpatients	Tardive dyskinesia severity and other EPS symptoms were assessed with AIMS and ESRS (Extrapyramidal Symptom Rating Scale) at baseline. Assessment of tardive dyskinesia severity was performed every 2 weeks to the endpoint/week 12 of study
Baker, 1996 United States Inpatients	NR

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Arato, 2002 Europe Inpatients	NR	Ziprasidone 40mg vs ziprasidone 80mg vs ziprasidone 160mg vs placebo Total withdrawals per group: 58% vs 57% vs 55% vs 86% Withdrawals due to AEs: 10% vs 10% vs 7% vs 15%
Bai, 2003 Taiwan Inpatients	No significant differences between the two groups in ESRS scores, mean change between baseline and endpoint for ESRS scores, or the % of concomitant antiparkinsonian and benzodiazepine use at the end of the study. Risperidone (n=22) vs placebo (n=20) group: AIMS change in mean score from baseline (SD): -5.5 (3.8) vs -1.1 (4.8), p=0.001 Mean change in ESPR-parkinsonian score at endpoint: -0.5 vs -0.3, p=NS Mean change in ESPR-dystonia score at endpoint: -0.5 vs -0.8, p=NS	7 ; 3
Baker, 1996 United States Inpatients	NR	NR

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
Beasley, 2003 Beasley, 2006 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	326 (224 olanzapine, 102 placebo)	4- to 9-day screening evaluation, 6-week conversion to open-label olanzapine, 8-week stabilization on olanzapine, and 52-week randomized double-blind maintenance with olanzapine or placebo.	Otherwise healthy outpatients ages 18-65 with schizophrenia or schizoaffective disorder. Minimal symptoms defined as a BPRS score of no more than 36 at baseline (with relatively little fluctuation of 4 weeks or longer prior to study entry); outpatient status; Global Assessment of Functioning score of 40 or greater; current maintenance on an antipsychotic agent other than clozapine at either 300 mg/d or more chlorpromazine equivalent for oral agents or 25 mg or more every 2 weeks of fluphenazine decanoate equivalent for injectable agents; lack of specific positive symptoms, as measured by a score of 4 or greater on the BPRS positive items (scored 1-7) of conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.
Borison, 1996 United States	109	Multicenter, BD, PCT	Men and women aged 18-60 years were eligible to enter the study if they satisfied DSM-III-R criteria for chronic or subchronic schizophrenia with acute exacerbation. Patients were also required to have a minimum total score of 45 on the 18-item BPRS (0-7 scoring), a score of 4 (moderate) on at least two items from the BPRS positive symptom cluster (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content), and a score of 4 (moderately ill) on the CGI Severity of illness item.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
Beasley, 2003 Beasley, 2006 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Olanzapine 10 mg, 15 mg, or 20 mg per day or placebo For 26-week maintenance period.	Screening period (skipped if patient was currently stable on a fixed dose of olanzapine monotherapy), 4- to 9-days, 6-week conversion to open-label olanzapine, 8-week stabilization on olanzapine	NR	Mean age 36 (SD 11) 53% male Ethnicity not reported
Borison, 1996 United States	Quetiapine 75mg-750mg/day or placebo for 6 weeks. But daily dosage greater than 500mg were limited to 14 days.	2-10 days placebo phase/NA	No	Mean age = 36 (18-58) years Gender: 91% male Ethnicity: 62% white; 36% black; 3% other

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
Beasley, 2003 Beasley, 2006 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Schizophrenic 79% olanzapine vs 87.3% placebo Schizoaffective 21% olanzapine vs 12.7% placebo	583/ 458/ 326	84 withdrawn/1 lost to followup/324 analyzed	BPRS, PANSS, Heinrichs-Carpenter Quality of Life Questionnaire
Borison, 1996 United States	Acute exacerbation: 47.4% chronic undifferentiated 35.5% chronic paranoid 16.5% other Previous hospitalization: 51.1% <8 57.9% >8 17.4% unknown	NR/ 146/ 109	59 (54.1%)/0/106	Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression (CGI) Modified Scale for the Assessment of Negative Symptoms (SANS)

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
Beasley, 2003 Beasley, 2006 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Patients formally evaluated at least every 2 weeks at the investigative site, at a home visit, or by telephone. Primary efficacy parameter was lack of relapse during the maintenance phase. Defined as (1) an increase in any BPRS positive item to >4, and either an absolute increase of 2 or more on that specific item from randomization at visit 16 or an absolute increase of 4 or more on the BPRS positive subscale from randomization at visit 16; or (2) hospitalization due to positive psychotic symptoms. Secondary efficacy assessments included the PANSS total and subscale scores. Quality of life measured by the Heinrichs-Carpenter Quality of Life Questionnaire
Borison, 1996 United States	Scales are rated by the trained investigators weekly

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
Beasley, 2003 Beasley, 2006 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Patients relapsing after 8 weeks of maintenance olanzapine: 9/224 (4.0%) vs placebo: 28/102 (27%), p<0.001 Mean worsening on PANSS from baseline after 8 weeks of maintenance (olanzapine vs placebo) Total score: 1.8 (+ 9.2) vs 17.7 (+ 19.1), p=0.002 Positive score: 0.6 (+ 2.9) vs 5.4 (+ 5.6), p=0.002 Negative score: 0.3 (+ 2.5) vs 3.4 (+ 4.9), p=0.064 General Psychopathology: 0.9 (+ 4.9) vs 9.2 (+ 10.3), p=0.002 Quality of Life (mean change in scale score): Olanzapine 4.25 vs placebo -7.11; p<0.001
Borison, 1996 United States	Quetiapine vs placebo (change from baseline), p value: BPRS total score: -8.1(2.39) vs -2.1(2.30), p=0.07 BPRS factor score: Anxiety/depression: -0.6(0.14) vs -0.6(0.14), p=0.75 Anergia: -0.1(0.14) vs 0.0(0.14), p=0.52 Thought disturbance: -0.7(0.18) vs -0.3(0.18), p=0.09 Activation: -0.4(0.18) vs 0.4(0.18), p=0.002 Hostile/suspiciousness: -0.4(0.22) vs 0.0(0.22), p=0.18 BPRS positive-symptom cluster score: -0.9(0.21) vs -0.3(0.21), p=0.06 CGI Severity of Illness item score: -0.2(0.18) vs 0.2(0.18), p=0.07 SANS summary score: -1.0(0.61) vs 0.6(0.6), p<0.05 CGI Global Improvement: improved: 28% vs 25%, p=0.02 worsened: 17% vs 42%

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
Beasley, 2003 Beasley, 2006 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Spontaneously reported adverse events collected; Simpson-Angus Scale, Barnes Akathisia Scale.
Borison, 1996 United States	Simpson Scale Abnormal Involuntary Movement Scale (AIMS)

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Beasley, 2003 Beasley, 2006 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Change from baseline to 8 weeks, olanzapine vs placebo: Simpson-Angus Scale: -0.11 (SD 0.96) vs 0.02 (SD 0.51) Barnes Akathisia Scale: -0.01 (SD 0.30) vs -0.03 (SD 0.33), p=NS Treatment-emergent parkinsonism : 0.9% vs 0, p=NS Treatment-emergent akathisia : 1.8% vs 2%, p=NS Tardive dyskinesia : 0.5% vs 2%, p= NS Treatment-emergent AEs with an incidence of >5% (olanzapine vs placebo) Anxiety: 6.7% vs 12.7% (p=0.088) Weight gain: 6.3% vs 1.0% (p=0.043) Thinking abnormal: 3.6% vs 7.8% (p=0.105) Schizophrenic reaction: 3.1% vs 25.5% (p<0.001) Hallucinations: 2.2% vs 6.9% (p=0.055) Apathy:1.8% vs 5.9% (p=0.077) Insomnia: 1.3% vs 19.6% (p=0.001) Paranoid reaction: 1.3% vs 10.8% (p=0.001) Weight loss: 0.9% vs 6.9% (p=0.005) Hostility: 0.4% vs 3.9% (p=0.035) Anorexia: 0.0% vs 2.9% (p=0.030)	13% olanzapine vs 54% placebo ; 1% olanzapine vs 12% placebo
Borison, 1996 United States	AIMS: NS	Withdrawn due to adverse events (no. patients): quetiapine 3 vs. placebo 2

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
Canuso, 2009 India, Russia, the Ukraine, and the United States	399	DB RCT	Inclusion: 18 to 65 years of age and had a diagnosis of schizophrenia (paranoid, disorganized, or undifferentiated types) according to DSM-IV criteria and confirmed by the MINI-Plus Version; experiencing an acute exacerbation for less than 4 weeks but more than 4 days and had symptom score ≥4 (at least moderate) on at least two of the PANSS items of hostility, excitement, tension, uncooperativeness, and poor impulse control, and a total combined score ≥17 for these items; a score of ≥5 (at least markedly ill) on the CGI-S and hospitalized or required hospitalization. Exclusion: DSM-IV axis I diagnosis (except for schizophrenia and substance abuse); an axis II diagnosis of mental retardation or borderline personality disorder; acute psychotic symptoms explained by substance use or medical illness; evidence for imminent risk of self-harm; a history of treatment resistance; treatment with quetiapine, paliperidone ER, or risperidone for ≥7 days prior to assessment for study entry; sensitivity to paliperidone ER, risperidone, or quetiapine; depot antipsychotic treatment within one cycle before baseline; and ECT within 3 months of entry.
Castle 2009 Multinational - 15 countries	2011	Prospective observational, multicenter	A diagnosis that met an indication for olanzapine (acute mania or schizophrenia) were inpatients, including Ers, required trmt with a short acting IM psychotic and were not enrolled in a clinical trial

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
Canuso, 2009 India, Russia, the Ukraine, and the United States	Monotherapy Phase (days 1-14) Paliperidone ER 6 mg (days 1-3); 9 mg (day 4), optional increase to 12 mg (day 8) Quetiapine 50mg/day (day 1); 100 mg/day (day 2); 200 mg/day (day 3); 400 mg/day (day 4); 600 mg/day (day 5), optional increase to 800 mg/day (day 8) Placebo Additive-therapy phase (days 15-42): Continued on dose received at day 14 with additional psychotropic medications allowed, including antipsychotics Mean daily dose were paliperidone ER 9.8 mg and quetiapine 599.1 mg	Day 0: discontinued all psychotropic medications	Monotherapy phase: injectable lorazepam, amobarbital sodium, or midazolam as needed for severe agitation or restlessness; zalephon, zopiclone, or zolpidem for insomnia; and benztropine mesylate or equivalent treatments for movement disorders. Additive-therapy phase: Any psychotropic medication, including antipsychotics permitted except for risperidone, additional paliperidone extended-release or quetiapine, and other specifically prohibited medications: drugs that interact with P450 isoenzyme CYP3A4, lithium, herbal/over-the-counter medications that have psychotropic effects, and drugs that prolong the QTc interval.	Paliperidone vs Quetiapine vs Placebo Mean age (SD): 35.7 (11.6) vs 36.9 (10.2) vs 36.1 (10.4) years Male: 66.9% vs 68.2% vs 62.5% Caucasian: 47.1% vs 43.9% vs 41.3% Asian: 36.3% vs 36.9% vs 38.8% Black: 14% vs 16.6% vs 20% Hispanic: 0.6% vs 1.3% vs 0 Other: 1.9% vs 1.3% vs 0
Castle 2009 Multinational - 15 countries	IM olanzapine vs. other IM antipsychotics	None	Antipsychotics and other concomitant medications	Mean age 36.3 yrs 51% male Ethnicity NR

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
Canuso, 2009 India, Russia, the Ukraine, and the United States	Paliperidone vs Quetiapine vs Placebo Mean age at onset of symptoms: 23.2 vs 25.2 vs 23.6 years Mean age at first diagnosis: 25.5 vs 26.8 vs 25.5 years Mean total PANSS score: 102.8 vs 101.3 vs 103.8 Mean CGI-S: 5.2 vs 5.2 vs 5.2	NR/NR/399	116/21/394	PANSS CGI-S and change scores of CGI Readiness for Discharge Questionnaire (based on behavioral and functional status) Medication Satisfaction Questionnaire
Castle 2009 Multinational - 15 countries	Schizophrenia 70.1% Acute mania 29.9%	2046/2011/2011	49/23/2011	PANSS-EC, CGI-S

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
Canuso, 2009 India, Russia, the Ukraine, and the United States	PANSS and CGI-S assessed on days 3, 5, 7, 9, 14, 21, 28, and 42, and at endpoint. Readiness for Discharge Questionnaire on days 3, 5, 7, 9, 14, 21. Medication Satisfaction Questionnaire on days 14 and 42
Castle 2009 Multinational - 15 countries	Reduction in PANSS-EC greater than 40% - response by investigator at 2 hrs after injection , then 24, 72 hours and 7 days

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
Canuso, 2009 India, Russia, the Ukraine, and the United States	Paliperidone vs Quetiapine vs Placebo Mean change in PANSS total score (SE) from baseline to day 14 [primary outcome measure]: -23.4 (1.8) vs -17.1 (1.8) vs -15.0 (NR); (*P*< 0.05 for paliperidone vs quetiapine or placebo) Mean change in CGI-S (SE) from baseline to day 42: NR For paliperidone vs quetiapine: -0.3 (0.1); *P* =0.002 For paliperidone vs placebo: -0.5 (0.1); *P* <0.001 For quetiapine vs placebo: -0.2 (0.1); *P* =NS Mean change in CGI change sore (SE) from baseline to day 42: NR For paliperidone vs quetiapine: -0.1 (0.1); *P* =0.002 For paliperidone vs placebo: -0.4 (0.2); *P* <0.001 For quetiapine vs placebo: -0.3 (0.2); *P* =NS Readiness for discharge rate: 50.6% vs 43.3% vs 37.5%; (*P* =0.027 for paliperidone vs placebo) Mean change in Medication Satisfaction Questionnaire (SE): 5.3 (0.1) vs 4.8 (0.1) vs 4.7 (0.2); (*P<0.05* for paliperidone vs quetiapine or placebo)
Castle 2009 Multinational - 15 countries	Olanzapine vs others (95% CI) 2 hrs post injection - change PANSS-EC mean -6.53 (-7.03, -6.02) vs. -5.71 (-6.27, -5.15) CGI-S -0.67 (-0.75, -0.59) vs. -0.56 (-0.65, -0.47)

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
Canuso, 2009 India, Russia, the Ukraine, and the United States	Treatment -emergent adverse events and vital signs monitored and recorded at each visit. Laboratory tests (hematology, biochemistry studies, prolactin levels, thyroid function tests, and urinalysis) and ECG conducted on days 0, 14, and 42. Movement disorders were assessed on days 0, 14, and 42 using the SAR-S, BARS, and AIMS.
Castle 2009 Multinational - 15 countries	Recorded by investigators

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Canuso, 2009 India, Russia, the Ukraine, and the United States	Paliperidone (n=158) vs Quetiapine (n=159) vs Placebo (n=80) Change in Simpson-Angus Scale total score (SE): -0.1 (0.2) vs -0.4 (0.2) vs 0.2 (0.3) Change in AIMS total score (SE): -0.1 (0.2) vs -0.2 (0.2) vs -0.2 (0.2) Change in maximum Barnes global severity subscore (SE): 0.1 (0.1) vs -0.2 (0.1) vs -0.1 (0.1) Change in prolactin value in males (SE): 16.2 (1.7) vs -4.1 (2.6) vs -1.9 (1.8) Change in prolactin value in females (SE): 60.4 (7.5) vs -12.7 (9.6) vs -9.0 (7.9) Patients with at least one AE: 119 (75.3%) vs 123 (77.4%) vs 54 (67.5%) Serious AE: 13 (8.2%) vs 7 (4.4%) vs 2 (2.5%) Constipation: 7 (4.4%) vs 12 (7.5%) vs 2 (2.5%) Diarrhea: 2 (1.3%) vs 8 (5%) vs 2 (2.5%) Dry mouth: 5 (3.2%) vs 10 (6.3%) vs 1 (1.3%) Dyspepsia: 4 (2.5%) vs 8 (5%) vs 4 (5%) Vomiting: 12 (7.6%) vs 10 (6.3%) vs 2 (2.5%) Asthenia: 10 (6.3%) vs 8 (5%) vs 6 (7.5%) Akathisia: 15 (9.5%) vs 10 (6.3%) vs 5 (6.3%) Dizziness: 6 (3.8%) vs 24 (15.1%) vs 1 (1.3%) Drooling: 13 (8.2%) vs 4 (2.5%) vs 1 (1.3%) Headache: 23 (14.6%) vs 19 (11.9%) vs 13 (16.3%) Hypertonia: 19 (12.0%) vs 6 (3.8%) vs 3 (3.8%) Sedation: 7 (4.4%) vs 17 (10.7%) vs 3 (3.8%) Somnolence: 18 (11.4%) vs 24 (15.1%) vs 2 (2.5%) Tremor: 31 (19.6%) vs 12 (7.5%) vs 12 (15%) Agitation: 7 (4.4%) vs 5 (3.1%) vs 4 (5%) Depressed mood: 4 (2.5%) vs 0 vs 4 (5%) Insomnia: 19 (12%) vs 16 (10.1%) vs 12 (15%) Schizophrenia: 9 (5.7%) vs 14 (8.8%) vs 10 (12.5%) One death in the placebo group.	Paliperidone (n=160) vs Quetiapine (n=159) vs Placebo (n=80) Withdrawals: 34 (21.3%) vs 53 (33.3%) vs 29 (36.3%) Withdrawals due to AE: 10 (6.3%) vs 16 (10.1%) vs 5 (6.3%)
Castle 2009 Multinational - 15 countries	Olanzapine vs.. Haloperidol vs. zuclopenthixol % patients with 1 or more AE 34.4 vs. 41.7 vs. 65.4 Akathisia 4.4 vs. 7.1 vs. 20.6 Disturbance in attention 7.0 vs. 7.3 vs. 7.5 Dystonia 2.3 vs. 8.7 vs. 7.5 Parkinsonism 5.8 vs. 11.5 vs. 9.3 Sedation 23.3 vs. 23.6 vs. 42.1	49 withdrawals due to AEs NR

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
Ciliberto, 2005 (see Kane 2003)	439 Caucasian 193 African-American 174 Other 72	Multicenter, DB, randomized, PCT	see Kane 2003
Cutler, 2006 United States	367	Randomized, DB, PCT, hospitalized subjects in 36 US sites, utilizing 3 fixed doses Multicenter	Male & female > 18yr age. Hospitalized patients with acute relapse of schizophrenia, shown a documented worsening of schizophrenia within 3 months. A positive and Negative syndrome scale (PAMSS) total score of >60 and a score of at least 4 on > 2 of PANSS items of delusions, hallucinatory behavior, conceptual disorganization suspiciousness. Evidence of responsiveness to antipsychotic medications (other than clozapine) in the past 2 years.
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	302 randomized	Randomized, DB, parallel group PCT Multicenter	Men or women ≥18 years with an acute exacerbation of chronic of subchronic schizophrenia or schizoaffective disorder as defined by DSM-III-R who had been hospitalized within the previous 4 weeks and who had a total score ≥60 on the PANSS with a score of ≥4 on 2 or more core items in the PANSS in the 24 hours before the study treatment was started. Also, patients had to have a score ≥3 on the CGI-I at baseline as compared with screening; their body weight had to be <=160% of the upper limit of normal according to sex, height, and frame; and their urine samples had to be negative for all illicit drugs except for investigator-given cannabinoids and benzodiazepines.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
Ciliberto, 2005 (see Kane 2003)	Long-acting risperidone 25 mg, 50 mg, and 75 mg placebo Intramuscular injection every 2 weeks for 12 weeks.	see Kane 2003	NR	Age: 37.6 yrs Males % Caucasian 72.5% African-American 68.4% Other 76.4% Ethnicity Caucasian: 44% African-American 39.6% Other 16.4%
Cutler, 2006 United States	aripiprazole 2mg/day aripiprazole 5mg/day aripiprazole 10mg/day Placebo	3-14 day screen which includes washout period of at least 3 days, which patient did not receive antipsychotic medications.	psychotropic drugs other than aripiprazole prohibited with the exception of lorazepam (max 4mg/day = anxiety or emergent agitation not w/in 4hr of safety or efficacy assessment), However zolpidem and zaleplon (non benzodiazepine medications) were allowed for insomnia. Additionally anticholinergic medications were permitted for EPS treatment but not 24 hours prior to randomization or within 12 hours of safety and efficacy rating assessment .	Mean age: 41.1 years 78.5% male 21.5% female 48.1% white 47% black/ African American 4.9% Other
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	Ziprasidone 80 mg/d (n=106) Ziprasidone 160 mg/d (n=104) placebo (n=92) 6-week study (no dosage adjustments after the first 2 days)	NR/ single-blind placebo washout lasting 3-7 days	Concomitant lorazepam (for insomnia or agitation), benzatropine (for EPS) , and beta-adrenoceptor antagonists (for akathisia) were allowed if required but were not administered prophylactically.	Mean age: Age range: 18-67 years 71.2% male 68.2% white 19.9% black 2.3% Asian 9.6% other

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
Ciliberto, 2005 (see Kane 2003)	Diagnosis (%) Schizophrenia Caucasian 86.0 African-American 96.0 Other 93.1 Schizoaffective disorder Caucasian 14.0 African-American 4.0 Other 6.9	NR/NR/429	248/ NR/ 429	CGI-S PANSS
Cutler, 2006 United States	Mean baseline PANSS total score: 90.9	NR/367/367	80/NR/195	PANSS total score, PEC Scores PANSS positive and negative factor scores, CGI scale.
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	Ziprasidone 80 vs ziprasidone 160 vs placebo: Schizoaffective disorder: 23% vs 24% vs 21% Disorganized schizophrenia: 3% vs 3% vs 3% Catatonic schizophrenia: 1% vs 1% vs 1% Paranoid schizophrenia: 50% vs 42% vs 49% Undifferentiated schizophrenia: 23% vs 32% vs 26% Baseline scores: PANSS total score: 98.2 vs 95.8 vs 97.3 PANSS negative score: 25.4 vs 24.3 vs 24.9 BPRSd total score: 56.5 vs 55.0 vs 55.1 CGI-S score: 4.8 vs 4.8 vs 4.8 MADRS total score (n=89, 100, and 100 respectively): 17.0 vs 16.9 vs 17.4	440/ NR / 302	Unclear / unclear / 298	PANSS, total and negative subscale scores MADRS BPRSd, total core items scores CGI-S CGI-I

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
Ciliberto, 2005 (see Kane 2003)	PANSS every 2 weeks, CGI every week.
Cutler, 2006 United States	Primary efficacy outcome measure was the mean change from baseline to endpoint (week 6 last observation carried forward [LOCF]) in PANSS total score. All groups were tested against 0.05 level baseline data were evaluated by analysis of variance w/treatment as a main effect. Compared with placebo at the end of the study(-11.3 vs -5 p=.030)
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	Efficacy variables, except for MADRS. were measured at baseline and weekly for 6 weeks or on early termination (within 24h of receiving the last dose). For CGI-I, the baseline value was based on the comparison with screening, and subsequent weekly assessments were based on comparisons with baseline. MADRS total score was assessed at baseline and weeks 1,2,3, and 6 (or early termination).

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
Ciliberto, 2005 (see Kane 2003)	Mean change in PANSS Active vs. Placebo Caucasian -7.8 vs. 0.8 (p≤0.05) African-American -11.5 vs. -6.1 (p≤0.05) Other -12.0 vs. 8.3 (p≤0.05) CGI-S not ill to mildly ill baseline/endpoint Active vs. placebo Caucasian 24.1% / 42.2% vs15.6% / 28.9% African-American 14.3% / 38.7% vs. 21.4% / 21.4% Other 2.4% / 45.2% vs. 15.4% / 15.4%
Cutler, 2006 United States	Aripiprazole vs placebo: Aripiprazole 10mg/day, patients improved from baseline for PANSS total at endpoint (-11.3 vs -5.3; P=0.3). At weeks 2-5 aripiprazole 5mg/day no greater improvement in PANSS total. Aripiprazole 2mg/day no statistically significant improvements.
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	ziprasidone 80 vs ziprasidone 160 vs placebo: Mean change in MADRS score from baseline: -1.8 vs -3.1 vs -1.3 % mean improvement from baseline at 6 weeks (ITT LOCF): p<0.05 for Z 80 and Z 160 vs placebo for all scores PANSS total: 12% vs 18% vs 5% BPRSd total: 6% vs 13% vs 18% BPRSd core item: 12% vs 20% vs 27% CGI-S: 4% vs 10% vs 17% PANSS negative subscale: 3% vs 12.5% vs 15.5%

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
Ciliberto, 2005 (see Kane 2003)	See Kane 2003
Cutler, 2006 United States	SAS, Barnes Akathisia (BAS), and the AIMS, vital signs, and EPS rating scales. ECG and laboratory tests.
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	All AE volunteered and observed during study and within 6 days of the last treatment were recorded. Safety assessments were performed at regular intervals or within 24h of early termination. SARS, Barnes Akathisia, and AIMS administered at baseline and week 6 for all (SARS and Barnes also assessed at weeks 1 and 3)

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Ciliberto, 2005 (see Kane 2003)	All AEs active vs. placebo (%) Caucasian 84.4 vs.82.7 African-American 80.2 vs.89.5 Other 80.0 vs. 70.6	Withdrawals Active vs. placebo (%) Caucasian 54.6 vs. 73.1 African-American 50.7 vs. 65.8 Other 49.1 vs. 70.6 Withdrawals due to AEs Active vs Placebo (%) Caucasian 15.6 vs. 13.5 African-American 7.4 vs. 10.5 Other 16.4 vs. 5.9
Cutler, 2006 United States	Treatment-emergent AE's reported in 68.5% subjects. Comparable across treatment vs placebo groups (70% in 10mg/day, 65% in 5mg/day. 71% in 2mg/day and 68% in placebo group). Most common was headache with placebo at 20.7% and mean treatment groups at 17.3%. Nausea showed a dose response increase from low of 5.4% in the 2mg/day to a high of 10.6% in the 10mg/day group as compared to 3.4% in the placebo group. Constipation, Back pain and upper abdominal pain had a higher incidence in the 10mg/day group.	n=172/n=13
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	Ziprasidone 80 vs ziprasidone 160 vs placebo Total % of patients with AEs: 87% vs 89% vs 86% % of patients with severe AEs: 8% vs 8% vs 11% % who took lorazepam at some point in study: 81% vs 87% vs 92% % who took benzatropine: 20% vs 25% vs 13% % who required beta-adrenoceptor antagonists: 9.4% vs 5.8% vs 6.5% Median changes in body weight: +1 kg vs 0kg vs 0kg Individual AEs: Pain: 6% vs 10% vs 9% Headache: 17% vs 31% vs 33% Abdominal pain: 3% vs 10% vs 5% Vomiting: 11% vs 6 % vs 15% Dyspepsia: 9% vs 14 % vs 9% Nausea: 14% vs 7% vs 9% Dry mouth: 4% vs 13% vs 4% Constipation: 7% vs 14% vs 14% Dizziness: 9% vs 17% vs 9% Agitation: 10% vs 9% vs 11% Insomnia:12% vs 12% vs 14% Somnolence: 19% vs 19% vs 5% Akathisia: 14% vs 13% vs 7%	Ziprasidone 80 vs ziprasidone 160 vs placebo Total % of patients who withdrew: unclear Total % of patients discontinued due to AEs: 1.8% vs 7.7% vs 1.1%

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
Kahn, 2007 Multinational	588	Multicenter, BD, PCT	Men and women 18-65 years, DSM-IV diagnosis acute schizophrenia PANSS of 70 or greater Exclusion DSM-IV diagnosis of another Axis 1 disorder: substance abuse; hospitalization for more than a month, recent dosing with depot; other clinically relevant diseases (i.e.. hepatic, renal, diabetes)
Kane, 2003 Nasrallah, 2004 United States	400	Multicenter, double-blind.	Hospital outpatients or inpatients ages 18-55 with a diagnosis of schizophrenia according to DSM-IV criteria; baseline PANSS total scores of 60-120 and good general health, with standard laboratory test results within reference ranges or not clinically significant.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
Kahn, 2007 Multinational	fixed-dose quetiapine XR 400, 600, or 800 mg/day (once daily in the evening), quetiapine immediate release (IR) 400 mg/day (200 mg twice daily), or placebo.	48 hour washout	Anticholinergic treatment for EPS allowed. At bed time - zolpidem, chloral hydrate, zaleplon and zopiclone. Also lorazepam and oxazepam during 1st 6 days	Mean age 34 years Gender- 60.2% male Ethnicity 59.2% white, 4.5% black, 36.1% Asian < 1% other
Kane, 2003 Nasrallah, 2004 United States	Long-acting risperidone 25 mg, 50 mg, 75 mg, or placebo intramuscular injection Every 2 weeks for 12 weeks.	1-week screening period, then doses of other oral antipsychotic medications were reduced and then discontinued. Simultaneously, oral risperidone started at 2 mg/day and increased to 4 mg/day for at least 3 days.	Oral risperidone or oral placebo continued for the first 3 weeks of the double-blind phase. Antiparkinsonian medications; restricted use of sedative medications (i.e., lorazepam, chloral hydrate, temazepam) allowed; antidepressants; Beta-blocking agents.	Mean age 38 (SD 10) 75% male 42% African American, 42% white, 11% Hispanic, 6% other ethnicity

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
Kahn, 2007 Multinational	DSM-IV schizophrenia subtype, % Disorganized=4.5 Catatonic=0.7 Paranoid=67.2 Undifferentiated=27.7 Schizophrenia history Age at diagnosis (mean yrs): 26.4 Time since diagnosis (mean yrs): 8.3 No. of episodes (mean): 4.8 Inpatients: 76.3% Baseline scores (mean) PANSS total=96.5 CGI-I=4.9	NR/NR/588	112/7/573	Clinical Global Impression (CGI) Negative Scale of the Positive and Negative Syndrome Scale (PANSS)
Kane, 2003 Nasrallah, 2004 United States	Schizophrenia subtype: 76% paranoid, 21% undifferentiated, 3% disorganized, <1% catatonic; 51% outpatients, 49% inpatients	554/ 461/ 400	206 withdrawn/17 lost to followup/370 analyzed	PANSS total score Secondary measures: PANSS positive and negative factor scores, CGI scale.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
Kahn, 2007 Multinational	PANNS and CGI-S weekly and CGI-I at week 6
Kane, 2003 Nasrallah, 2004 United States	PANSS every 2 weeks, CGI every week; trained raters, interrater reliability established before the start of the trial. SF-36 measured HRQoL (Health Related Quality of Life) consisting of 8 domains; a score above 50 is a score above normative average. SF-36 assessed at baseline and 12-week endpoint (or study discontinuation)

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
Kahn, 2007 Multinational	Mean change in PANSS 400XR -31.1 600XR -35.1 800XR -37.7 400IR -33.1 Placebo -23.1 All vs. placebo P< 0.05 CGI-I response rate (%) 400XR 73.9 600XR 79.3 800XR 76.9 400IR 75.6 Placebo 60 All vs. placebo P< 0.05 Change in CGI-S 400XR -1.3 600XR -1.5 800XR -1.6 400IR -1.3 Placebo -1.0
Kane, 2003 Nasrallah, 2004 United States	Mean change at endpoint on PANSS (LOCF): Total score placebo: 2.6 risperidone 25 mg: -6.2 (p=0.002 vs placebo) risperidone 50 mg: -8.5 (p<0.001 vs placebo) risperidone 75 mg: -7.4 (p<0.001 vs placebo) Positive symptoms placebo: -0.2 risperidone 25 mg: -2.3 (p=0.05 vs placebo) risperidone 50 mg: -3.5 (p<0.001 vs placebo) risperidone 75 mg: -3.0 (p<=0.005 vs placebo) Negative symptoms placebo: 0.9 risperidone 25 mg: -2.4 (p<0.001 vs placebo) risperidone 50 mg: -1.2 (p=0.02 vs placebo) risperidone 75 mg: -1.2 (p=0.02 vs placebo) Mean change at endpoint on CGI (LOCF), placebo vs R 25 vs R 50 vs R 75: 0.3 vs -0.3 vs -0.3 vs -0.4 (p<0.001 for all comparisons vs placebo) Mean change from baseline on the SF-36 scale (HRQoL measure) Risperidone (all doses) vs placebo p<0.05 for 5 of 8 domains: Bodily pain, General health, Social functioning, Role-emotional, Mental health p=NS between any risperidone group vs placebo for Vitality and Physical Functioning (2 of 8) domains Risperidone 25 mg vs placebo, p<0.05 for Role-Functioning domain (1 of 8); other Risperidone doses NS

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
Kahn, 2007 Multinational	BAS, Simpson-Angus Scale, lab measures and MedRA measures of somnolence and EPS
Kane, 2003 Nasrallah, 2004 United States	Assessed at baseline and every 2 weeks. Serious adverse events were defined as those that resulted in death or were life-threatening, required hospitalization or prolongation of hospitalization, resulted in persistent or significant disability or incapacity, or resulted in a congenital anomaly or birth defect. Spontaneously reported extrapyramidal symptoms (extrapyramidal disorder, hyperkinesia, hypertonia, tremor, hypokinesia, and involuntary muscle contractions). Severity of extrapyramidal symptoms evaluated by 55-item Extrapyramidal Symptom Rating Scale (ESRS). Investigators trained in the use of the ESRS, and interrater reliability was established before the trial.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Kahn, 2007 Multinational	Placebo, 400XR, 600XR, 800XR, 400IR Overall AEs (%) 42.4, 45.1, 54.9, 46.3, 53.7 Drug related AEs (%) 12.7, 20.4, 30.1, 22.3, 22.0 Serious AEs (%) 1.7, 1.8, 2.7, 0.8, 4.9 leading to discontinuation (%) 2.5, 5.3, 2.7, 2.5, 4.9 Insomnia (%) 19.5, 11.5, 6.2, 7.4, 10.6 Somnolence (%) 1.7, 7.1, 8.8, 11.6, 7.3 Dizziness (%) 0.8, 5.3, 8.8, 6.6, 5.7 Headache (%) 6.8, 5.3, 3.5, 3.3, 1.6 Sleep disorder (%) 9.3, 3.5, 5.3, 3.3, 4.9 Constipation (%) 4.2, 1.8, 5.3, 4.1, 0.8	Total withdrawals 142 % by treatment groups placebo 28 400XR 26.5 600XR 18.6 800XR 25.6 400 IR 22.0 due to AEs 21 % by treatment groups placebo 2.5 400XR 5.3 600XR 2.7 800XR 2.5 400 IR 4.9
Kane, 2003 Nasrallah, 2004 United States	Risperidone 25 mg vs 50 mg vs 75 mg vs placebo Any AE: 80% vs 83% vs 82% vs 83% Serious AEs: 13% vs 14% vs 15% vs 23.5% 1 death in placebo group due to injury Mean change from baseline to 12 weeks on ESRS (all comparisons NS): Total: -1.5 vs 0.1 vs 0.0 vs -0.1 Parkinsonian subscale -1.1 vs 0.0 vs 0.3 vs -0.5 Dystonia subscale : 0.0 vs 0.0 vs 0.0 vs 0.0 Dyskinesia subscale -0.4 vs 0.1 vs -0.3 vs 0.4 Spontaneously reported AEs related to EPS: risperidone 25 mg: 10% risperidone 50 mg: 24% risperidone 75 mg: 29% placebo: 13% (p>0.10 for all groups vs placebo)	Overall withdrawals: risperidone 25 mg: 52% risperidone 50 mg: 51% risperidone 75 mg: 52% placebo: 68% Withdrawals due to AEs: risperidone 25 mg: 11% risperidone 50 mg: 12% risperidone 75 mg: 14% placebo: 12%

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
Keck, 1998 United States	139 randomized	Randomized, DB, PCT Multicenter	Men or women aged 18-64 years with an acute exacerbation of chronic or subchronic schizophrenia or schizoaffective disorder as defined in DSM-III-R who had been hospitalized within the previous 3 weeks with a minimum duration of illness of 1 year. At screening and 24h before study, patients had to have a total score ≥37 on the BPRS and a score of ≥4 on 2 or more of the PBPRS core items. Patients were generally no more than 140% of the upper limit of normal weight according to sex, age, height, and frame, and urine samples had to be negative for all illicit drugs except cannabinoids and benzodiazepines.
Kramer, 2007 United States, Romania, Turkey, Latvia, Lithuania, and India	207	Randomized, double-blind, placebo-controlled, multicenter study	Inclusion- Men and women, 18 to 65 years; diagnosis of schizophrenia for at least 1 year ; experiencing an acute episode of schizophrenia PANSS total score, 70–120; physically healthy, capable of being compliant with self-administration of medication or have consistent help available throughout the study, and able to complete self-administered questionnaires. Exclusion- diagnosis other than schizophrenia, if they had a DSM-IV Axis I diagnosis of substance dependence (except nicotine or caffeine) within 6 months; significant risk of suicidal or aggressive behavior; medical conditions that could potentially alter the absorption, metabolism, or excretion; relevant history of significant or unstable disease; known allergic reactions to barbiturates, carbamazepine, lamotrigine, phenytoin, paliperidone, or risperidone; a previous lack of response to risperidone; used a depot antipsychotic within 120 days; exposure to experimental treatment within 90 days; electroconvulsive treatment within 3 months; or had involuntary admission to a psychiatric hospital; pregnant, nursing, or planning to become pregnant.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
Keck, 1998 United States	Ziprasidone 40 mg/d (n=44) Ziprasidone 120 mg/d (n=47) placebo (n=48) 4-week study	NR/ single-blind placebo washout lasting 4-7 days	Concomitant lorazepam (for insomnia or agitation), benzatropine (for EPS) , and beta-adrenoceptor antagonists (for akathisia) were allowed as required but were not administered prophylactically.	Mean age: 39.4 years Age range: 19-76 years 79.1% male 71.9% Caucasian 19.4% Black 3.6% Asian 5.0% other
Kramer, 2007 United States, Romania, Turkey, Latvia, Lithuania, and India	Open-label paliperidone ER (3– 15 mg once daily, starting dose = 9 mg) until stable (minimum of 2 weeks); a 6-week open-label stabilization phase; a double-blind treatment phase of variable duration, paliperidone ER (starting at the dose maintained during stabilization) or placebo	8-week run-in and a 6-week stabilization phases	Oral benztropine or biperiden (or equivalent agents) for the treatment of extrapyramidal symptom (EPS) control and b-adrenergic blockers for treatment-emergent akathisia. Antidepressants were allowed (excluding monoamine oxidase inhibitors) if the dose was stable for at least 3 months.	Mean age = 41 years 51% men, Ethnicity 85% white

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
Keck, 1998 United States	Ziprasidone 40 vs ziprasidone 120 vs placebo Schizoaffective disorder: 39% vs 43% vs 31% Disorganized schizophrenia: 2% vs 4% vs 2% Paranoid schizophrenia: 43% vs 38% vs 50% Undifferentiated schizophrenia: 14% vs 15% vs 17% Delusional disorder: 2% vs 0% vs 0% Neurologic illness at screening: 12.8% vs 8.5% vs 22.9%	203/ NR / 139	69/ 1/ 131	BPRS total score BPRS core item score CGI-S SANS total score BPRS depression cluster BPRS anergia factor score
Kramer, 2007 United States, Romania, Turkey, Latvia, Lithuania, and India	Mean age at schizophrenia diagnosis (yrs)=26.4 PANSS Total=52.2 CGI-S (%) Not ill=5.4 Very mild=50.2 Moderate=9.7 Days since last psychotic episode=195.7 Previous hospitalizations for psychosis (N): None=25.8% One=14.1% Two or more=60%	628/530 /530	351/NR/207	PANSS CGI-S

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
Keck, 1998 United States	Primary efficacy determined by BPRS total score and core items score and by CGI-S score. Secondary efficacy assessments made by CGI-I. SANS, the BPRS depression cluster score, the BPRS anergia cluster score.
Kramer, 2007 United States, Romania, Turkey, Latvia, Lithuania, and India	The primary efficacy variable was the time to first recurrence during the double-blind phase via (1) psychiatric hospitalization; (2) increase in PANSS total score by 25% for 2 consecutive days for patients who scored more than 40 at randomization or a 10-point increase for patients who scored 40 or below at randomization; (3) increase in CGI-S score to at least 4, for patients who scored 3 or below at randomization, or to at least 5, for patients whose CGI-S scores were 4 at randomization, for 2 consecutive days; (4) deliberate self-injury or aggressive behavior, or suicidal or homicidal ideation and aggressive behavior that was clinically significant; (5) increase in prespecified individual PANSS item scores to at least 5, for patients whose scores were 3 or below at randomization, or to at least 6, for patients whose scores were 4 at randomization, for 2 consecutive days.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
Keck, 1998 United States	Ziprasidone 40 vs ziprasidone 120 vs placebo: Percentage of patients who complete the study: 64% vs 51% vs 50% Mean change in score from baseline (*=p<0.01 for ziprasidone 120 vs placebo): BPRS total score: -5.2 vs -10.1* vs -4.1 BPRS core item score: -2.6 vs -4.1 vs -2.3 CGI-S: -0.4 vs -0.6 vs -0.2 SANS total score: -8.66 vs-7.4 vs -2.4 BPRS depression cluster: -3.0 vs -5.6* vs -2.6 BPRS anergia factor score:-1.4 vs -1.8* vs 0.3 % of patients who too adjunctive therapy during treatment: Benzatropine: 7% vs 19% vs 8% Lorazepam: 82% vs 85% vs 90% Beta-adrenoceptor antagonists: 7% vs 6% vs 4%
Kramer, 2007 United States, Romania, Turkey, Latvia, Lithuania, and India	14 paliperidone ER–treated patients (25%) experienced a recurrence event versus 29 (53%) for placebo Change in mean PANSS from baseline- Placebo 15.1 (19.1) vs. paliperidone 6.0 (13.6)* Change in median CGI-S from baseline (range)- Placebo 1.0 (-2 to 4) vs. paliperidone 0.0 (-2 to 3)*

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
Keck, 1998 United States	SARS, Barnes Akathisia, and the AIMS, vital signs, and clinical lab tests assessed at baseline and throughout study to endpoint.
Kramer, 2007 United States, Romania, Turkey, Latvia, Lithuania, and India	treatment emergent adverse events (TEAEs) (using the World Health Organization Adverse Reaction Terminology dictionary), clinical laboratory tests, vital sign measurements, body weight, physical examinations, 12-lead electrocardiograms, and movement disorder rating scales (Simpson Angus Scale, Barnes Akathisia Rating Scale, and Abnormal Involuntary Movement Scale). Serum prolactin was also measured.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Keck, 1998 United States	77% of all patients experienced AEs Ziprasidone 40 vs ziprasidone 120 vs placebo Mean change in these scores from baseline: SARS: -1 vs -1 vs -0.5 Barnes Akathisia: -0.1 vs -0.2 vs -0.2 AIMS: -0.3 vs -0.1 vs -0.2 % of patients experiencing an AE by group: 75% vs 81% vs 75% Pain: 9.1% vs 4.2% vs 8.3% Asthenia: 2.3% vs 4.2% vs 0% Headache: 18.2% vs 21.3% vs 20.8% Abdominal pain: 11.4% vs 2.1% vs 8.3% Dyspepsia: 11.4% vs 6.4% vs 6.3% Nausea: 6.8% vs 6.4% vs 4.2% Constipation: 6.8% vs 10.6% vs 4.2% Agitation: 0% vs 6.4% vs 12.5% Somnolence: 6.8% vs 8.5% vs 8.3% Akathisia: 6.8% vs 2.1% vs 6.3% Rash: 6.8% vs 2.1% vs 0%	Total number of withdrawals for all groups: 69 (45%); withdrawals due to AEs: 5 (3.6%)
Kramer, 2007 United States, Romania, Turkey, Latvia, Lithuania, and India	open-label phases all TEAEs (73%) tremor (16%), headache (14%), hyperkinesias (12%), and insomnia (10%). EPS (31%) During blinded phase placebo vs. paliperidone: all TEAEs 40% vs 35%. Psychosis 23% vs.7% Aggressive reaction 6% vs.1% Insomnia 6% vs. 5% EPS 3% vs. 7%	Total withdrawals 28 due to AEs 4

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
Lauriello, 2005 United States subanalysis of inpatients from Kane 2003	214 inpatients of original 439 patients	Multicenter, DB, randomized, PCT	see Kane 2003
Lauriello 2008 USA, Russia and Croatia	404	DB RCT Multicenter	18-75 years old, male or female, with a diagnosis of schizophrenia and a PANSS BPRS of 30 or more Exclusion- previously experienced clinically significant AEs during trmt with olanzapine, significant suicide or homicide risk, pregnancy or lactation, acute, serious or unstable medical conditions or substance abuse (except tobacco or caffeine) within last 30 days
Lindenmayer, 2005 (see Kane, 2003)	439	Multicenter, DB, randomized, PCT	see Kane 2003

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
Lauriello, 2005 United States subanalysis of inpatients from Kane 2003	Long-acting risperidone 25 mg, 50 mg, and 75 mg placebo Intramuscular injection every 2 weeks for 12 weeks.	see Kane 2003	Permissible medications for sleep were temazepam, zolpidem or chloral hydrate. Limited doses of lorazepam were permitted for agitation, with max. weekly dose of 42mg during first 2 weeks following randomization, a max. weekly dose of 38mg during the following 2 weeks and a max. weekly dose of 16mg thereafter.	Mean age = 38 years Gender: 70% male Ethnicity: 42.6% Caucasian; 41.5% black; 24.5% Hispanic; 4.7% other
Lauriello 2008 USA, Russia and Croatia	210 mg/2 weeks, 300 mg/2 weeks, or 405 mg/4 weeks of olanzapine LAI or placebo/2 weeks for 8 weeks	2-7 day screening/washout	Multiple benzodiazepines/sedatives and anticholinergics	Mean 41 yrs 71% male 56% White
Lindenmayer, 2005 (see Kane, 2003)	Long-acting risperidone 25 mg, 50 mg, and 75 mg placebo Intramuscular injection every 2 weeks for 12 weeks.	see Kane 2003	See Kane 2003	Mean age 38 (SD 10) 75% male 42% African American, 42% white, 11% Hispanic, 6% other ethnicity

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
Lauriello, 2005 United States subanalysis of inpatients from Kane 2003	Schizophrenia: 91.1% Schizoaffective disorder: 8.8% Prior treatment with antipsychotic: 67.4%	NR/ NR/ 214 inpatients	140/ NR/ 74 inpatients	see Kane 2003
Lauriello 2008 USA, Russia and Croatia	94% previous use of 1 or more antipsychotics	466/440/404	137/3/402	PANSS, BPRS, CGI-S and CGI-I
Lindenmayer, 2005 (see Kane, 2003)	See Kane 2003	NR/NR/429	NR/ NR/ 429	Patient VAS and investigator evaluation

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
Lauriello, 2005 United States subanalysis of inpatients from Kane 2003	PANSS every 2 weeks, CGI every week.
Lauriello 2008 USA, Russia and Croatia	PANSS assessed at baseline, days 3 and 7 and then weekly
Lindenmayer, 2005 (see Kane, 2003)	Patients 100-mm Visual Analogue Scale (VAS) for pain (ratings from 0=no pain, to 100=unbearably painful) immediately after each injection and 2 weeks post-injection. Investigators rated injection site pain, redness, swelling and induration as absent, mild, moderate or severe after the first and final injections.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
Lauriello, 2005 United States subanalysis of inpatients from Kane 2003	long-acting risperidone (all risperidone groups together) vs placebo Mean change in PANSS total score: -17.06(1.88) vs -4.73(4.5), p=0.014 % of patients with PANSS >20% reduction in total scores: 50% vs 27%, p=0.012 % of patients with PANSS >40% reduction in total scores: 23% vs 5%, p=0.01 % of patients with CGI assessment of ill, very mild or mild: 32% vs 5%, p=0.0023
Lauriello 2008 USA, Russia and Croatia	Olanzapine 210 mg/2 weeks vs. 300 mg/2 weeks vs. 405 mg/4 weeks vs. Placebo Change in mean (sd) Total PANSS -22.5 (21.8)* vs. -26.3 (24.9)* vs. -22.6 (22.1)* vs. -8.5 (23.0) PANSS positive -6.3 (6.8)* vs. -7.4 (7.8)* vs. -7.2 (6.9)* vs. -2.0 (7.6) PANSS negative -4.8 (5.6)* vs. -6.3 (6.2)* vs. -4.6 (5.4)* vs. -2.1 (5.8) PANSS general psychopathology -11.4 (11.5)* vs. -12.6 (12.8)* vs. -10.8 (11.4)* vs. -4.4 (12.0) BPRS -14.1 (11.5)* vs. 16.4 (14.3)* vs. 14.5 (13.9)* vs. 6-.0 (13.6) CGI-S -0.6 (1.1)** vs. -0.6 (1.2)*** vs. -0.6 (1.1)* vs. -0.3 (1.1) * vs. placebo P < 0.001 ** vs. placebo P = 0.003 *** vs. placebo P = 0.001
Lindenmayer, 2005 (see Kane, 2003)	Mean±SD VAS scores at first and final injections placebo vs. risperidone 15.6±20.7 and 12.5±18.3 vs. 11.8±14.4

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
Lauriello, 2005 United States subanalysis of inpatients from Kane 2003	Adverse events assessed every 2 weeks, by investigators. Pain at site of injection assessed by VAS (scale: 0=no pain to 100=unbearable pain)
Lauriello 2008 USA, Russia and Croatia	Patient reported AEs using MEDRA , labs, EPS with BAS, SAS and AIMs
Lindenmayer, 2005 (see Kane, 2003)	See Kane 2003

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Lauriello, 2005 United States subanalysis of inpatients from Kane 2003	ESRS score: NS Long acting risperidone vs placebo: AEs related to movement disorders: 12% vs 15% Mean change in body weight: +2.3kg vs -0.43kg, p=0.0003 Patient-reported injection site pain on VAS (SD): 12.3(20.01) vs 6.71(12.81), NS Concomitant medications: 93% vs 89%, NS Antiparkinsonian agents taken by 27% vs 21%patients. Antidepressants taken by 14% vs 9% patients.	Total inpatients who withdrew: 140/214 Withdrawals by group: risperidone vs placebo inpatients: 60% (96/161) vs 83% (44/53) Withdrawals due to AEs: risperidone 14% vs placebo 11%
Lauriello 2008 USA, Russia and Croatia	Olanzapine 210 mg/2 weeks vs. 300 mg/2 weeks vs. 405 mg/4 weeks vs. Placebo % Headache 15.1 vs. 17.0 vs. 11.0 vs. 8.2 Insomnia 11.3 vs. 11.0 vs. 10.0 vs. 14.3 Sedation 6.6 vs. 10.0 vs. 8.0 vs. 2.0 Constipation 6.6 vs. 6.0 vs. 6.0 vs. 12.0 Agitation 5.7 vs. 5.0 vs. 8.0 vs. 11.2 Weight gain 5.7 vs. 7.0 vs. 5.0 vs. 5.1 Cough 4.7 vs. 9.0 vs. 3.0 vs. 5.1 Diarrhea 6.6 vs. 5.0 vs. 2.0 vs. 4.1 Anxiety 2.8 vs. 2.0 vs. 5.0 vs. 6.1 Back pain 2.8 vs. 5.0 vs. 4.0 vs. 4.1 Dyspepsia 3.8 vs. 3.0 vs. 3.0 vs. 5.1 Nausea 4.7 vs. 4.0 vs. 5.0 vs. 2.0 Somnolence 0.9 vs. 3.0 vs. 6.0 vs. 5.1 Dry mouth 5.7 vs. 4.0 vs. 2.0 vs. 1.0 Paranoia 2.8 vs. 1.0 vs. 2.0 vs. 7.1 Psychotic disorder 1.9 vs. 1.0 vs. 4.0 vs. 6.1 Delusion 1.9 vs. 2.0 vs. 2.0 vs. 6.1 Nasopharyngitis 5.7 vs. 1.0 vs. 3.0 vs. 2.0 Increased appetite 3.8 vs. 6.0 vs. 1.0 vs. 0 Vomiting 0.9 vs. 2.0 vs. 6.0 vs. 2.0	137 withdrawals 18 due to AEs
Lindenmayer, 2005 (see Kane, 2003)	See primary results for injection site pain	52% withdrew

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
Luthringer, 2007 Europe (Poland, France, and Romania)	42	RCT DB	Men and women (ages 18–45 years), with schizophrenia and schizophrenia related insomnia were eligible; symptomatically stable [Positive and Negative Syndrome Scale (PANSS) score at most 90] with no history of relapse or acute psychotic symptoms for at least 3 months; required to have a regular sleep/wake schedule, but to complain of at least 1.5 h of wakefulness per 8 h in bed and to be willing to provide a sleep history. Female patients were required to be postmenopausal for 2 years, to be surgically sterile, or to be using birth control methods. Exclusion -any other concomitant Axis I DSM-IV diagnosis other than schizophrenia and schizophrenia- related insomnia, meeting DSM-IV criteria for psychoactive substance dependence within 3 months, suicidal or violent behavior either currently or in the preceding 6 months, any other sleep disorder diagnosis, and the presence of any medical condition that could potentially alter the absorption, metabolism, or excretion of the study medication.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
Luthringer, 2007 Europe (Poland, France, and Romania)	9 mg paliperidone ER or matching placebo 14 days	7 day washout- 3 day baseline period	Yes	Mean age 32.2 years (range 20-46) Gender- 67% male Ethnicity 97% white

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
Luthringer, 2007 Europe (Poland, France, and Romania)	Schizophrenia type (%) Paranoid=50 Undifferentiated=22 Residual=28 Days since last psychotic episode=314 Age at first schizophrenia diagnosis (yrs)=24.1 Total PANSS=62.9 CGI-S (%) Very mild=8 Mild=58 Moderate=28 Marked=6	56/NR/42	6/NR/36	sleep architecture and sleep continuity were evaluated using polysomnograms. Subjective sleep measures were evaluated daily using the Leeds Sleep Evaluation Questionnaire. Also PANSS and CGI-S

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
Luthringer, 2007 Europe (Poland, France, and Romania)	Two electroencephalogram channels (C3A2 and C4A1), bilateral electro-oculograms, and two submental electromyograms. At baseline and nights 14 and 15

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
Luthringer, 2007 Europe (Poland, France, and Romania)	Patients relapsing after 8 weeks of maintenance olanzapine: 9/224 (4.0%) vs placebo: 28/102 (27%), p<0.001 Mean worsening on PANSS from baseline after 8 weeks of maintenance (olanzapine vs placebo) Total score: 1.8 (+ 9.2) vs 17.7 (+ 19.1), p=0.002

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
Luthringer, 2007 Europe (Poland, France, and Romania)	Reported adverse events, clinical laboratory tests (hematology, serum chemistry, and urinalysis), electrocardiograms, vital signs, physical examinations, and ratings on the Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, and Simpson-Angus Rating Scale.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Luthringer, 2007 Europe (Poland, France, and Romania)	Placebo vs. paliperidone n (%) Total no. of patients with adverse events 11 (52) vs.13 (62), Central and peripheral nervous system disorders 3 (14) vs. 8 (38), Dystonia 0 vs. 2 (10), Extrapyramidal disorder 0 vs. 2 (10), Headache 0 vs. 2 (10), Oculogyric crisis 0 vs. 2 (10), Dyskinesia 0 vs. 1 (5), Hyperkinesia 2 (10) vs. 1 (5), Vertigo 0 vs. 1 (5), Hypertonia 1 (5) vs. 0, Psychiatric disorders 5 (24) vs. 4 (19) Insomnia 0 vs. 1 (5), Nervousness 1 (5) vs. 1 (5), Psychosis 2 (10) vs. 1 (5), Somnolence 2 (10) vs. 1 (5), Personality disorder 1 (5) vs. 0, Suicide attempt 1 (5) vs. 0, Gastrointestinal system disorders 3 (14) vs. 2 (10), Abdominal pain 0 vs. 1 (5), Dyspepsia 1 (5) vs. 1 (5), Vomiting 1 (5) vs. 1 (5), Nausea 2 (10) vs. 0, Platelet, bleeding and clotting disorders 0 vs. 2 (10) Epistaxis 0 vs. 1 (5), Thrombocytopenia 0 vs. 1 (5), Cardiovascular disorders, general 0 vs. 1 (5), Hypertension 0 vs. 1 (5), Hearing and vestibular disorders 0 vs. 1 (5), Earache 0 vs. 1 (5) Hearing decreased 0 vs. 1 (5), Metabolic and nutritional disorders 1 (5) vs. 1 (5), Hyperglycemia 1 (5) vs. 1 (5), Musculo-skeletal system disorders 0 vs. 1 (5), Skeletal pain 0 vs. 1 (5) Resistance mechanism disorders 0 vs. 1 (5), Infection viral 0 vs. 1 (5), Body as a whole-general disorders 2 (10) vs. 0, Back pain 1 (5) vs. 0, Pain 1 (5) vs. 0, Reproductive disorders, female 1 (5) vs. 0, Dysmenorrhea 1 (5) vs. 0, Skin and appendages disorders 1 (5) vs. 0, Dermatitis contact 1 (5) vs. 0, Rash 1 (5) vs. 0	6 and 6

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
Marder, 2007 USA Funding Johnson & Johnson	444	RCT DB	Inclusion - At leas 18 years of age and experiencing an acute episode of schizophrenia, represented by a Positive and Negative Syndrome Scale (PANSS) total score of 70–120; diagnosed with schizophrenia according to DSM-IV criteria for 1 year before screening and to have agreed to voluntary hospitalization for at least 14 days. Exclusion criteria included diagnosis of substance dependence within the previous 6 months; medical conditions affecting absorption, metabolism, or excretion of the study drug; history of tardive dyskinesia or neuroleptic malignant syndrome; being at significant risk of suicide or violent behavior; female patients who were pregnant or breast-feeding; patients receiving a depot antipsychotic within 120 days or paliperidone palmitate as part of a clinical trial within 10 months before screening; and use of antidepressants or mood stabilizers within 2 weeks before screening. A history of drug sensitivity or allergy, including hypersensitivity to risperidone, paliperidone, or olanzapine, or a history of unresponsiveness to antipsychotic agents

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
Marder, 2007 USA Funding Johnson & Johnson	Placebo vs. Paliperidone ER 6mg/day vs. Paliperidone ER 12 mg/day vs. Olanzapine 10 mg/day for 6 weeks	5 day washout	Predefined doses of benzodiazepines for the treatment of agitation, anxiety or sleep difficulties. Antidepressant use was permitted for patients on stable dosages for 3 months	Mean age 41.6 years 74% male

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
Marder, 2007 USA Funding Johnson & Johnson	63% at least markedly ill on CGI-S	444/444/432	252/28/432	PANSS; CGI-S, Marder, PSP

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
Marder, 2007 USA Funding Johnson & Johnson	Total PANSS and Marder factor scores and Clinical Global Impression–Severity (CGI-S) scores were assessed at baseline; days 4, 8, and 15; and then every 7 days up to and including day 43. PSP scale, was assessed at baseline and endpoint

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
Marder, 2007 USA Funding Johnson & Johnson	Placebo vs. Paliperidone ER 6mg vs. Paliperidone ER 12 mg vs. Olanzapine PANSS Total Score Change from Baseline -8.0 (21.5) vs. -15.7 (18.9) vs. -17.5 (19.8) vs. -18.4 (19.9) Difference in LS Means N/A vs. -7.0 (2.4) vs. -8.5 (2.4) vs. AS p Value vs. Placebo - NA vs. 0.006 vs. <0.001 vs. AS Patients with a 30% Reduction PANSS Total Score (%) 34 vs. 50 vs. 51 vs. 45.7 p Value vs. Placebo - NA vs. 0.025 vs. 0.013 vs. AS Patients with a 50% Reduction PANSS Total Score (%) 31.4 vs. 40.9 vs. 46.8 vs. 41.9 p Value vs. Placebo - NA vs. .180 vs. 0.016 vs. AS AS=Assay sensitivity only CGI-S scale with paliperidone ER compared with placebo (p = .009 for paliperidone ER 6 mg; p < 0.001 for paliperidone ER 12 mg).

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
Marder, 2007 USA Funding Johnson & Johnson	report of AEs at every scheduled visit. Treatment-emergent glucose-, prolactin-, and extrapyramidal symptom– related AEs were defined using World Health Organization Adverse Reaction Terminology preferred terms. Movement disorders were assessed using the report of AEs and: Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson–Angus Rating Scale (SAS), evaluated at baseline, days 8 and 15, and then every 7 days up to and including day 43. and clinical laboratory evaluations and physical exams

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Marder, 2007 USA Funding Johnson & Johnson	Placebo vs Paliperidone vs. Olanzapine n (%) Total Number of Patients with Adverse Events 82 (77) vs. 171 (76) vs. 79 (72) Central and Peripheral Nervous System Symptoms Headache 20 (19) vs. 53 (24) vs. 12 (11) Dizziness 11 (10) vs. 16 (7) vs. 8 (7) Hyperkinesia 5 (5) vs. 14 (6) vs. 1 (1) Extrapyramidal Disorder 4 (4) vs. 9 (4) vs. 2 (2) Hypertonia 2 (2) vs. 9 (4) vs. 0 Psychiatric Symptoms Somnolence 14 (13) vs. 30 (13) vs. 30 (28) Insomnia 13 (12) vs. 27 (12) vs. 9 (8) Agitation 11 (10) vs. 19 (8) vs. 11 (10) Anxiety 10 (9) vs. 17 (8) vs. 5 (5) Psychosis 13 (12) vs. 13 (6) vs. 10 (9) Gastrointestinal System Symptoms Dyspepsia 11 (10) vs. 25 (11) vs. 12 (11) Mouth dry 1 (1) vs. 12 (5) vs. 2 (2) Nausea 10 (9) vs. .11 (5) vs. 7 (6) Constipation 10 (9) vs. 10 (4) vs. 5 (5) Vomiting 7 (7) vs. 10 (4) vs. 4 (4) Toothache 3 (3) vs. 7 (3) vs. 5 (5) Body as a Whole—General Symptoms Pain 7 (7) vs. 7 (3) vs. 2 (2) Respiratory Symptoms Upper Respiratory Tract Infection 4 (4) vs. 9 (4) vs. 3 (3) Cardiovascular Symptoms, General Electrocardiogram Abnormal Specific 5 (5) vs. 9 (4) vs. 6 (6) Heart Rate and Rhythm Symptoms Tachycardia 3 (3) vs. 12 (5) vs. 4 (4) Musculoskeletal System Symptoms Skeletal Pain 1 (1) vs. 9 (4) vs. 1 (1) Skin and Appendage Symptoms Rash 5 (5) vs. 0 vs. 1 (1)	Total withdrawals 252 (57%) Due to AEs 8 (2%)

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
McEvoy, 2007 USA	420	RCT DB Multicenter	Male and female participants; 18 y or older with a diagnosis of schizophrenia (DSM-IV criteria); experiencing an acute exacerbation of symptoms that required inpatient hospitalization; PANSS Total score of 60 or more and a score of at least 4 on two or more of the following PANSS items at the baseline assessment: delusions, hallucinatory behavior, conceptual disorganization or suspiciousness/persecution. Prior responsiveness to antipsychotic medication; treated as an outpatient for at least one continuous 3-month period during the preceding 12 months. Female patients were required to use adequate contraception for the duration of the study Exclusion- psychiatric disorder other than schizophrenia, a history of recent suicidal attempts or suicidal intentions; significant substance abuse disorder within the previous 3 months; neuroleptic malignant syndrome or had been hospitalized for more than 14 days prior; fluoxetine or an investigational drug within 4 weeks prior to randomization or benzodiazepines in the 2 weeks prior to randomization.
Peuskens, 2007 Bulgaria, India, Poland, Russia, and Ukraine	327 stabilization 197 randomized	RCT DB Multicenter	Inclusion if ≥18 to ≤65 years; a documented clinical diagnosis of schizophrenia (according to DSM-IV]) for at least two years; clinically stable before entering the stabilization phase (defined as a CGI-S score ≤4 and unchanged treatment [both compound and dose] with antipsychotic agent[s] within four weeks prior to entering the study); and a Positive and Negative Syndrome Scale (PANSS) total score ≤60 at enrollment Exclusion if treatment with depot antipsychotics within one dosing interval before enrollment (Week 16); pregnancy or breastfeeding; any DSM-IV Axis 1 disorder not defined in the inclusion criteria; any clinically significant deviations from the reference range in clinical laboratory test results at enrollment, as evaluated by the investigator; intolerance or lack of response to quetiapine; previous treatment with clozapine and/or valproic acid within two months of enrollment; and history of nonadherence

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
McEvoy, 2007 USA	Placebo vs. aripiprazole (10 mg/day, 15 mg/day and 20 mg/day) 6 weeks with escape at 3 weeks	Wash out of at least 2 days (median 7 days)	Anticholinergic treatment was allowed for EPS and lorazepam	Mean age: 40.4 years 78% male Ethnicity NR
Peuskens, 2007 Bulgaria, India, Poland, Russia, and Ukraine	Quetiapine XR (flexibly dosed at 400–800mg/day) or placebo, following a 16-week, open-label stabilization phase	16-week, open-label stabilization phase	None reported	Mean age: 35 years 60% male Ethnicity NR

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
McEvoy, 2007 USA	Mean body weight 83.8 kg Mean (SE) age at time of first hospitalization for schizophrenia 24 years	508/420/420	278/10 /410	PANSS (Total score, Positive subscale and Negative subscale) and CGI scales , the PANSS-derived Brief Psychiatric Rating Scale (BPRS) Core score was calculated from the scores for the following items from the PANSS: delusions, conceptual disorganization, hallucinatory behavior and suspiciousness/persecution.
Peuskens, 2007 Bulgaria, India, Poland, Russia, and Ukraine	Age at first diagnosis: 26.5 years Years since diagnosis: 8.7 Number of schizophrenia episodes: 4.3	NR/NR/327 enrolled/197 randomized	NR/NR/197	PANSS score, Clinical Global Impression-Improvement (CGI-I)

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
McEvoy, 2007 USA	The primary efficacy parameter was the mean change from baseline in PANSS Total score to Week 6 ([LOCF]). The key secondary efficacy measures were the mean change from baseline to the end of the study in PANSS Negative score and PANSS derived BPRS Core score.
Peuskens, 2007 Bulgaria, India, Poland, Russia, and Ukraine	Time to first schizophrenia relapse after randomization. Relapse was defined as at least one of the following: hospitalization due to worsening schizophrenia, increase in PANSS score of ≥30 percent from baseline, Clinical Global Impression-Improvement (CGI-I) score ≥6 (much worse or very much worse), or a need for additional antipsychotic medication to treat psychosis (as determined by the investigator). Assessments were evaluated at each visit

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
McEvoy, 2007 USA	Placebo aripiprazole 10 aripiprazole 15 aripiprazole 20 Change in PANSS score Total 2.33 15.04*** 11.73** 14.44*** 12.71 Positive 1.10 4.98*** 3.81** 4.51*** 3.88 Negative 0.08 3.52*** 2.65** 3.33*** 3.60 PANSS-derived BPRS Core score 1.37 3.91*** 2.88* 3.56*** Mean CGI-S scores 0.18 0.65** 0.51* 0.64** 0.47 Mean CGI-I score 4.00 3.33** 3.42** 3.31** Responders, n (%) 28 (26) 42 (41)* 36 (35) 44 (45)** * p < 0.05 vs. placebo. ** p < 0.01 vs. placebo. *** p < 0.001 vs. placebo.
Peuskens, 2007 Bulgaria, India, Poland, Russia, and Ukraine	The risk of a relapse was reduced by 84 percent (HR 0.16, p<0.0001) in the quetiapine XR-treated patients compared with placebo-treated patients The risk of relapse at six months, estimated by Cox regression analysis, was significantly lower in the quetiapine XR group (14.3%) than in the placebo group (68.2%; p<0.0001

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
McEvoy, 2007 USA	Adverse events (AEs) were recorded throughout; extrapyramidal symptoms were evaluated at baseline and each study visit using the Simpson–Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS), and at baseline and the end of Weeks 2, 4 and 6 using AIMS. Vital signs and prolactin levels were also measured at specific time points. Twelve-lead electrocardiogram (ECG) measurements and laboratory tests were assessed at screening, and at the end of Weeks 3 and 6.
Peuskens, 2007 Bulgaria, India, Poland, Russia, and Ukraine	Patient reported AEs and withdrawals during the stabilization and double-blind randomization phases and during the first two weeks after enrollment. Laboratory measurements, including hematology, clinical chemistry (P-glucose, S-insulin, and HbA1c), lipids, thyroid function, and urinalysis, were made at enrollment, every four weeks during the stabilization phase (excluding urinalysis), and at baseline, Month 3, Month 6, Month 9, and Month 12 of the randomization phase.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events	Total number of withdrawals; withdrawals due to adverse events
McEvoy, 2007 USA	(n (%)) Any adverse event placebo 66(62) aripiprazole10 67(64) aripiprazole15 76(72) aripiprazole20 72(74) Agitation placebo 22 (21) aripiprazole10 9 (9) aripiprazole15 13 (12) aripiprazole20 12 (12) Headache placebo 16 (15) aripiprazole10 24 (23) aripiprazole15 18 (17) aripiprazole20 32 (33) Insomnia placebo 13 (12) aripiprazole10 10 (10) aripiprazole15 22 (21) aripiprazole20 18 (18) Dyspepsia placebo 13 (12) aripiprazole10 12 (11) aripiprazole15 13 (12) aripiprazole20 12 (12) Anxiety placebo 13 (12) aripiprazole10 7 (7) aripiprazole15 13 (12) aripiprazole20 7 (7) Nausea placebo 9 (9) aripiprazole10 12 (11) aripiprazole15 15 (14) aripiprazole20 23 (23) Somnolence placebo 6 (6) aripiprazole10 7 (7) aripiprazole15 12 (11) aripiprazole20 10 (10) Constipation placebo 6 (6) aripiprazole10 5 (5) aripiprazole15 7 (7) aripiprazole20 9 (9) Extrapyramidal syndrome placebo 6 (6) aripiprazole10 4 (4) aripiprazole15 3 (3) aripiprazole20 2 (2) Asthenia placebo 6 (6) aripiprazole10 5 (5) aripiprazole15 7 (7) aripiprazole20 3 (3) Lightheadedness placebo 5 (5) aripiprazole10 7 (7) aripiprazole15 7 (7) aripiprazole20 13 (13) Vomiting placebo 4 (4) aripiprazole10 6 (6) aripiprazole15 7 (7) aripiprazole20 15 (15) Diarrhea placebo 4 (4) aripiprazole10 2 (2) aripiprazole15 2 (2) aripiprazole20 9 (9) Akathisia placebo 3 (3) aripiprazole10 10 (10) aripiprazole15 6 (6) aripiprazole20 5 (5)	278 withdrawals, 25 due to AEs
Peuskens, 2007 Bulgaria, India, Poland, Russia, and Ukraine	Stabilization phase Somnolence 19.3% Dizziness 6.4% Randomization phase Serious AEs placebo 1.9% quetiapine 0% Insomnia placebo 17.5% quetiapine 8.5% Headache placebo 4.9% quetiapine 7.4%	80 withdrawals (61 due to relapse) 2 withdrawals during stabilization phase and 2 during randomization phase were due to AEs

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
Pigott, 2003 International	310 (n=155 in aripiprazole and n=155 in placebo groups)	Randomized, DB, parallel-group, PCT Multicenter	Stabilized male and female patients ≥18 diagnosed with schizophrenia as defined by DSM-IV criteria for at least 2 years prior to study with a baseline PANSS ≥60, a score ≤4 on the subscale for hostility or uncooperativeness, and a score ≤4 on the CGI-S.
Small, 1997 United States and Europe	286	Multicenter, DB, PCT	Hospitalized men and women aged 18-65 years were eligible to enter the study if they satisfied DSM-III-R criteria for chronic or subchronic schizophrenia with acute exacerbation . Patients were also required to have a minimum total score of 45 on the 18-item BPRS (0-7 scoring), a score of 4 (moderate) on at least two items from the BPRS positive symptom cluster (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content), and a score of 4 (moderately ill) on the CGI Severity of illness item.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
Pigott, 2003 International	Aripiprazole 15 mg/d placebo 26 weeks	NR/ 3-day washout for preexisting antipsychotic medication and any psychotropic medication.	Anticholinergic treatment for EPS allowed. Lorazepam, up to a max. of 4 mg/d, was allowed for emergent agitation if deemed necessary; and an additional 1-2 mg was allowed at night as a sleep aid.	Mean age: 42.0 years 56.1% male 90.6% white 6.5% black 0.6% Asian/Pacific Islander 2.3% Hispanic/Latino
Small, 1997 United States and Europe	Quetiapine low dose (<250mg/day), high dose (251-750mg/day) or placebo for 6 weeks. But the daily maximum dosage 750mg were limited to 14 days.	2 days placebo/NA	Chloral hydrate allowed for insomnia (500-1000mg at bedtime) and acute agitation (500mg) but was limited to 2000 mg/day. Lorazepam (1-2mg orally or intramuscularly) was permitted orally or intramuscularly for severe agitation or insomnia unresponsive to chloral hydrate or dose escalation of quetiapine. In Europe, other benzodiazepines were permitted within protocol-specific guidelines for frequency of use and maximum dose. Neither chloral hydrate nor lorazepam was permitted within 6 and 12 hrs of efficacy assessments. During the DB phase, benztropine mesylate was permitted by treatment of EPS, with the dose and duration specified by the treating clinician.	Mean age: 22.3 years Gender: 71.2% male Ethnicity: 70.7% white; 19.3% black; 10% others

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
Pigott, 2003 International	Mean baseline PANSS total score: 81.8	NR/ NR/ 310	194/ 2/ 297	CGI-I CGI-S PANSS PANSS-BPRS
Small, 1997 United States and Europe	Acute exacerbation: 29.3% chronic undifferentiated 54.6% chronic paranoid 12.6% disorganized 2.6% other Previous hospitalization: 52.3% <8 47.6% >8 5.9% unknown	NR/ NR/ 286	NR/ NR/ 280	Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression (CGI) Modified Scale for the Assessment of Negative Symptoms (SANS) Negative Scale of the Positive and Negative Syndrome Scale (PANSS)

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
Pigott, 2003 International	Primary outcome measure: Relapse=Clinical Global Impressions-Global Improvement scale (CGI-I) score of ≥ 5, Positive and Negative Syndrome Scale (PANSS) ≥ 5 on the subscore items of hostility or uncooperativeness on 2 successive days; or a ≥ 20% increase in PANSS total score **Secondary outcome measures:** number of patients who relapsed, time to relapse or discontinuation due to lack of efficacy or an adverse event CGI-S and CGI-I 7-point scales administered at weeks 1, 2, 3, 4, 6, 8, 10, 14, 18, 22 and 26 PANSS administered at weeks 3, 6, 10, 18 and 26
Small, 1997 United States and Europe	BPRS, CGI and SANS in the US or PANSS in Europe at on days 7, 14, 21, 28, 35 and 42

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
Pigott, 2003 International	Aripiprazole vs placebo: % of patients without relapse at week 26: 62.6% vs 39.4%, p<0.001 Relative risk of relapse with aripiprazole vs placebo: 0.50 (95% CI=0.35 to 0.71) % of patients who met criteria in analysis of secondary endpoints for relapse: 33.8% vs 57% Mean change in scores from baseline: PANSS: -2.08 vs +4.50, p≤0.01 CGI-I: +3.74 vs +4.47, p≤0.01 CGI-S: +0.15 vs +0.40, p≤0.05
Small, 1997 United States and Europe	Primary measure: BPRS total score: High Q- -8.7(1.64), <0.001 vs Placebo Low Q- -4.2(1.62), 0.04 vs High Q Placebo- -1.0(1.61), 0.15 vs Low Q CGI Severity of Illness: High Q- -0.6(0.13), 0.003 vs Placebo Low Q- -0.3(0.13), 0.08 vs High Q Placebo- -0.1(0.13), 0.23 vs Low Q Secondary measure: BPRS positive-symptom cluster score: High Q- -0.9(0.13), 0.03 vs Placebo Low Q- -0.6(0.13), 0.11 vs High Q Placebo- -0.4(0.13), 0.17 vs Low Q CGI Global Improvement (endpoint): High Q- 3.4(1.7), 0.006 vs Placebo Low Q- 4.0(1.7), 0.03 vs High Placebo- 4.1(1.8), 0.55 vs Low Q SANS summary score: High Q- -1.7(0.47), 0.02 vs Placebo Low Q- 0.3(0.48), 0.004 vs High Q Placebo- -0.1(0.46), 0.54 vs Low Q PANSS(N) total score: High Q- -4.4(1.2), 0.1 vs Placebo Low Q- -2.9(1.1), 0.32 vs High Q Placebo- -1.9(1.1), 0.52 vs Low Q

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
Pigott, 2003 International	SAS Barnes AIMS
Small, 1997 United States and Europe	Simpson-Angus Scale Barnes Akathisia Scale: Abnormal Involuntary Movement Scale

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Pigott, 2003 International	SAS : -0.85 vs -0.45, p≤0.05 Barnes: -.07 vs -0. 5, p=NS AIMS: -0.23 vs -0.26, p=NS	Total number of discontinuations per group: 54.2% vs 71.0% Withdrawals due to AEs: 10.3% vs 8.4%
Small, 1997 United States and Europe	Simpson-Angus Scale total score: NS Barnes Akathisia Scale: NS Abnormal Involuntary Movement Scale total score: NS	Withdrawals due to adverse events, no. of patients: High Q vs Low Q vs Placebo = 7 vs 7 vs 3

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria
Tzimos 2008 International (South Africa, Czech Republic, Greece, Russia, Slovakia, and Ukraine)	114	DB RCT Multicenter (21)	Men and women, aged 65 years and older, diagnosis of schizophrenia for at least one year and were experiencing an acute episode of schizophrenia (Positive and Negative Syndrome Scale [PANSS] total score of 70–120). Exclusion - axis I diagnosis other than schizophrenia, substance dependence (except nicotine or caffeine) within six months, or were considered a significant risk of suicidal or aggressive behavior; medical conditions that could potentially alter the absorption, metabolism, or excretion of the study medication; a relevant history of significant or unstable disease; known allergic reactions to barbiturates, carbamazepine, lamotrigine, phenytoin, paliperidone, or risperidone; a previous lack of response to risperidone; use of a depot antipsychotic within 120 days; exposure to experimental treatment within 90 days; ECT within three months; involuntary admission to a psychiatric hospital.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity
Tzimos 2008 International (South Africa, Czech Republic, Greece, Russia, Slovakia, and Ukraine)	Flexibly dosed paliperidone ER (3–12 mg) or placebo once daily 6 weeks	Up to 5 days washout/screening	Oral benzodiazepines; Oral benztropine or biperiden; adrenergic blockers; Beta-adrenergic blockers; Antidepressants (excluding monoamine oxidase inhibitors)	Mean age 70 yrs 26% male 99% white

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales
Tzimos 2008 International (South Africa, Czech Republic, Greece, Russia, Slovakia, and Ukraine)	97% prior psychotropic use	131/NR/111	24/NR/111	PANSS total and factor scores, Clinical Global Impressions Scale–Severity score (CGI-S), Personal and Social Performance Scale (to assess patient functioning), and the Schizophrenia Quality of Life Scale.

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Method of outcome assessment and timing of assessment
Tzimos 2008 International (South Africa, Czech Republic, Greece, Russia, Slovakia, and Ukraine)	Assessed days 0, 4, 8, 15, 22, 29, 36, and 43

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Results
Tzimos 2008 International (South Africa, Czech Republic, Greece, Russia, Slovakia, and Ukraine)	Placebo vs. Paliperidone ER PANSS change 9.9 (15.0) vs. 14.6 (14.6) P = 0.014 Change in median CGI-S 0.0 (-2, 2) vs. -0.5 (-3, 2) P = 0.105 Change in Personal and Social Performance Scale 4.7 (9.8) vs. 4.8 (10.7) P = 0.889 Change in Schizophrenia Quality of Life Scale 6.0 (15.3) vs. 9.0 (14.9) P = 0.561

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Methods of adverse event assessments
Tzimos 2008 International (South Africa, Czech Republic, Greece, Russia, Slovakia, and Ukraine)	Patient reported, clinical laboratory tests (routine tests plus serum prolactin, insulin, and C-peptide), vital sign measurements, body weight, physical examinations, 12-lead electrocardiograms, and movement disorder rating scales

Evidence Table 5. Placebo-controlled trials in patients with schizophrenia

Author, year Country Trial name	Adverse events		Total number of withdrawals; withdrawals due to adverse events
Tzimos 2008 International (South Africa, Czech Republic, Greece, Russia, Slovakia, and Ukraine)	Placebo vs. Paliperidone ER , n (%)		27 withdrawals 6 due to AEs
	All TEAEs 27 (71) vs. 51 (67)	Possibly related TEAE 17 (45) vs. 38 (50)	
	TEAE leading to death 2 (5) vs. 0	Any serious TEAE 3 (8) vs. 2 (3)	
	TEAE leading to discontinuation 3 (8) vs. 5 (7)		
	Nervous system disorders 9 (24) vs. 22 (29)	Extrapyramidal disorder 4 (11) vs. 4 (5)	
	Somnolence 2 (5) vs. 7 (9)	Dizziness 0 vs. 5 (7)	
	Headache 1 (3) vs. 4 (5)	Cardiac disorders 5 (13) vs. 20 (26)	
	Tachycardiac 0 vs. 12 (16)	Psychiatric disorders 9 (24) vs. 11 (14)	
	Insomnia 4 (11) vs. 7 (9)	Agitation 2 (5) vs. 2 (3)	
	Anxiety 2 (5) vs. 2 (3)	Investigations 5 (13) vs. 7 (9)	
	Electrocardiographic QTc interval prolonged 1 (3) vs. 5 (7)		
	Electrocardiographic T-wave inversion 2 (5) vs. 1 (1)		
	Gastrointestinal disorders 7 (18) 7 (9)		
	Nausea 2 (5) vs. 2 (3)	Vomiting 2 (5) vs. 1 (1)	
	General disorders 2 (5) vs. 5 (7)	Asthenia 2 (5) 4 (5)	
	Fatigue 0 vs. 1 (1)		
	Infections and infestations 6 (16) vs. 8 (11)		
	Nasopharyngitis 1 (3) vs. 0	Pneumonia 1 (3) vs. 1 (1)	
	Vascular disorders 2 (5) vs. 8 (11)	Hypertension 1 (3) vs. 4 (5)	
	Hypotension 0 vs. 4 (5)		

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Controlled studies			
Advokat, 2004 United States	Hospital charts and medical records from the Eastern Louisiana Mental Health System	Retrospective	September 1996 through September 2001
Advokat, 2003	Eastern Louisiana Mental Health System	Retrospective	1995-2001

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Controlled studies		
Advokat, 2004 United States	NR	Olanzapine: 20.6mg/day Risperidone: 5.3mg/day Quetiapine: 320.6mg/day Clozapine: 375mg/day
Advokat, 2003	5 years	olanzapine 332 days risperidone 376 days quetiapine 558 days clozapine 583 days

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Controlled studies				
Advokat, 2004 United States	Patients reporting initial baseline value of 35 or greater on the Brief Psychiatric Rating Scale (BPRS) and had at least 3 successive monthly BPRS ratings	Olanzapine/Risperidone/Quetiapine/ Clozapine Mean age (years): 39.8/41.2/43.3/ 38.7 %male: 37/22/36/29 %African-American: 50/47/45/71	NR/NR/100	NR/NR/100
Advokat, 2003	Schizoaffective/Bipolar Type, Paranoid Schizophrenia, or Schizophrenia Undifferentiated	Mean age=40.6 years 31% male 50% Africa American	398/100/100	NR/NR/100

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Controlled studies	
Advokat, 2004 United States	Maximum daily dosages 28 of 46 patients on olanzapine received 15mg or less per day as max dose 21 of 36 patients on risperidone received 4mg or less per day as max dose 8 of 11 patients on quetiapine received 400mg or less per day as max dose 7 of 7 patients on clozapine received 450mg or less per day as max dose Average Length of stay in hospital Olanzapine: 332 days Risperidone: 376 days Quetiapine: 558 days Clozapine: 583 days 20% or more change from baseline on BPRS Olanzapine: 33 of 46 (72%) patients Risperidone: 16 of 36 (44%) patients Quetiapine: 4 of 11 (36%) patients Clozapine: 5 of 7 (71%) patients Response latency Olanzapine: 1.67 months Risperidone: 1.47 months Quetiapine: 2.00 months Clozapine: 2.75 months
Advokat, 2003	length of hospitalization: olanzapine (n=18) vs risperidone (n=9) = 634 days vs 1017 days, p=0.038 >20% decline from baseline in BPRS score: olanzapine = 33/46 (72%) risperidone = 16/36 (44%) clozapine = 52/59 (88%) clo vs ris, p<0.01; ola vs ris, p=0.012; clo vs ola, p=0.034 responders that retained or improved their BPRS scores: olanzapine vs risperidone, NS Latencies from responders: olanzapine vs risperidone = 1.67 vs 1.47 months

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Controlled studies		
Advokat, 2004 United States	NR	
Advokat, 2003	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Agelink, 2001 Germany	Evangelical Hospital Gelsenkirchen, Germany	Retrospective	Mean: 14.1 days
Akkaya 2007 Turkey	Medical record review: Psychiatry Outpatient Clinic of Uludag University Medical Faculty	Retrospective	January 1998 to October 2005
Al-Zakwani, 2003 United States	Multicenter, United States	Retrospective	24 months

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Agelink, 2001 Germany	NR	amisulpride: 400 mg/day, olanzapine: 20 mg/day, sertindole: 12 mg/day, clozapine: 100 mg/day
Akkaya 2007 Turkey	Risperidone/Haloperidol/Olanzapine Mean duration of treatment (d): 430.7±536.7/761.5±836.7/754.5±818.9	Risperidone/Haloperidol/Olanzapine Mean dose (mg): 3 ±1.4/5.4±5.1/11.7±5.4
Al-Zakwani, 2003 United States	18 months	Doses not reported. Interventions-Typical Antipsychotics: chlorpromazine, haloperidol, thioridazine, perphenazine, other; Atypical Antipsychotics: risperidone, olanzapine, quetiapine, clozapine

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Agelink, 2001 Germany	Medication-free inpatients with schizophrenia	Mean age: 33.7 years 68.8% Male Ethnicity NR	NR/NR/51	0/0/51
Akkaya 2007 Turkey	Patients diagnosed with schizophrenia and placed on drug treatment	Risperidone/Haloperidol/Olanzapine Age (y): 34.5±13.5/34.6±12.5/32.5±14.8 Gender (% male): 57.1/58.2/60 Ethnicity: NR	NR 407 274	NR NR 189 (63 risperidone, 91 haloperidol, 35 olanzapine)
Al-Zakwani, 2003 United States	Psychosis, neurotic, personality and sexual disorders, drug/alcohol dependence, psychological malfunction arising from mental disorders, depressive disorder, childhood emotional disturbance/developmental delays, mental retardation/Alzheimer's/Parkinson's diseases	Mean age: 38.5 years 59% Male Ethnicity NR	2710/833/469	NR/NR/469

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Agelink, 2001 Germany	NR
Akkaya 2007 Turkey	Risperidone/Haloperidol/Olanzapine Rates of discontinuation (%) over 18 months 68.3/51.6/54.3 Relapse under treatment (%) No: 81/68.1/65.7 Yes: 19/31.9/34.3 Relapse resulting in hospitalization (%) No: 33.3/44.6/41.7 Yes: 66.7/55.2/58.3 Reason of treatment discontinuation (%) Compliance issues: 74.6/72.5/60 Side effect: 4.8/5.5/8.6 Relapse: 4.8/11/5.7 Hospitalization: 1.6/3.3/8.6 Treatment continued: 14.3/7.7/17.1
Al-Zakwani, 2003 United States	Typical Antipsychotics: # dose adjustments: 14(16.5%) # treatment augmentation: 1(1.2%) # requiring treatment switch: 11(12.9%) # receiving mixed therapy: 1(1.2%) Atypical Antipsychotics: # dose adjustments: 128(30.4%) # treatment augmentation: 3(0.8%) # requiring treatment switch: 70(18.2%) # receiving mixed therapy: 7(1.5%)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Agelink, 2001 Germany	clozapine, olanzapine, sertindole had a prolonged mean frequency-corrected QTc times; P<0.05 HRr at endpoint: A: 77.2 vs O: 84.6 vs S: 88.7 vs C: 95.9 CVr at endpoint: A: 3.9 vs O: 3.9 vs S: 5.2 vs C: 2.3	
Akkaya 2007 Turkey	Risperidone/Haloperidol/Olanzapine Side effects that caused treatment discontinuation (authors do not report if this figure is n or %) EPS: 0/5/2 Prolactin increase: 2/0/0 Weight gain: 0/0/1 Sedation: 1/0/0	
Al-Zakwani, 2003 United States	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Ascher-Svanum, 2004 Faries, 2005 USA	U.S. Schizophrenia Care and Assessment Program (US SCAP)	Prospective	July 1997 to 2003
Ascher-Svanum 2008 US (21 sites in multiple states)	Data from a randomized, open-label study of the cost effectiveness of olanzapine, risperidone, and typical antipsychotics. Twenty sites in the US.	Retrospective	May 1998-September 2002
Barak, 2004 Israel	Abarbamel Mental Health Center, Bat-Yam	Retrospective	January 1998 to December 2002

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Ascher-Svanum, 2004 Faries, 2005 USA	One year	Olanzapine Risperidone
Ascher-Svanum 2008 US (21 sites in multiple states)	One year	olanzapine 13.3 mg risperidone 4.85 mg typical antipsychotics: perphenazine, haloperidol, loxapine, thiothixene, fluphenazine, trifuloperazine, mesoridazine, thioridazine, chlorpromazine, molindone
Barak, 2004 Israel	5 years	clozapine 445mg for 575 days olanzapine 17.8mg for 492 days risperidone 4.6mg for 466 days

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Ascher-Svanum, 2004 Faries, 2005 USA	DSM-IV criteria for schizophrenia, schizoaffective, or schizophreniform disorder; ≥ 18 years; and understood and provided informed consent. Excluded if participation in a controlled clinical drug trial in past month .	Age at enrollment, Olanzapine 43.5 Risperidone 39.3 Male, Olanzapine 62.9% Risperidone 54.5% Ethnicity White Olanzapine 52.8% Risperidone 49.1% Black Olanzapine 41.5% Risperidone 39.1% Other Olanzapine 5.7% Risperidone 11.8%	NA	NR/NR/Olanzapine n = 159 Risperidone n = 112
Ascher-Svanum 2008 US (21 sites in multiple states)	18 years of age or older, DSM-IV criteria for schizophrenia, schizoaffective or schizophreniform disorders, minimum scoreof 18 on BPRS.	Mean age 43 years 63% male 54% white, 34% African American, 12% other race/ethnicity	664 664 648 (222 olanzapine, 217 risperidone, 209 typical antipsychotics)	None reported None reported 648
Barak, 2004 Israel	Schizophrenia or schizoaffective disorder with attempted suicide in the 4 weeks preceding admissions	Mean age=39.1 years 84.7% male Ethnicity: NR	68000/4486/378	NR/NR/378

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Ascher-Svanum, 2004 Faries, 2005 USA	Adherent group (n = 271) Hospitalization rates risperidone 24.1% vs. olanzapine 14.4% P = 0.040 Hospitalization days risperidone 14.5 days vs. olanzapine 9.9 days P = 0.035. Adherent and non-adherent groups combined (n = 516) Hospitalization rates risperidone 31.5% vs. olanzapine 23.6% P = 0.045 Hospitalization days risperidone 17.6 days vs. olanzapine 19.1 days P = 0.755. Odds of staying on monotherapy during the 1-year period (versus initiating polytherapy) (Faries 2005) Olanzapine versus quetiapine: OR 2.08 (95% CI 1.30, 3.31) Olanzapine versus risperidone: OR 1.36 (95% 1.01, 1.84)
Ascher-Svanum 2008 US (21 sites in multiple states)	Mean time (SD) to all-cause medication discontinuation: Olanzapine: 277.2 days (123.9); p<0.001 vs typical antipsychotics; p<0.001 vs risperidone; Risperidone: 231.9 days (142.2) Typical antipsychotics: 193.5 days (137.9) Perphenazine: 277.2 days (123.9) One-year survival rates (SD): Olanzapine: 55.3% (3.6%); p=0.007 vs risperidone Risperidone: 46.8* (3.5%) Typical antipsychotics: 31.7% (3.3%); p <0.001 vs olanzapine; p=0.002 vs risperidone Perphenazine: 30.8% (6.8%); p<0.001 vs olanzapine; p=0.060 vs risperidone
Barak, 2004 Israel	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Ascher-Svanum, 2004 Faries, 2005 USA	NR	
Ascher-Svanum 2008 US (21 sites in multiple states)	NA	
Barak, 2004 Israel	suicide group vs control group exposed to second generation antipsychotics: 16% vs 37%, p=0.0001 protective effect: OR (p, 95% CI) overall: 3.54 (p=NR, 2.4-5.3) risperidone: 3.16 (p=0.001, 1.9-5.3) olanzapine: 1.76 (p=0.02, 1.2-3.3)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Barner, 2004 United States	Database: Central Texas Veterans Health Care System	Retrospective	Duration of treatment NR. Mean number of persistent days (total number of continuous days the patient took an antipsychotic agent without a gap, I.e. a 15-day lapse in therapy): AAPs: 3.9-5.6 months Typical APs: 4.7-7.3 months
Bitter, 2005 Africa, the Middle East, Asia, Central and Eastern Europe, Latin America IC-SOHO Study (6-month data) Hostile/aggressive behavior outcomes	same as Dossenbach 2004	same as Dossenbach 2004	same as Dossenbach 2004
Bond, 2004 United States	A psychiatric rehabilitation agency and four community mental health centers.	Prospective	March 1999 to January 2001
Brown, 2005 United States	Review of charts of VA patients	Retrospective	June 2001 to March 2003

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Barner, 2004 United States	NR	Any AAP or typical AP, dose and duration not reported
Bitter, 2005 Africa, the Middle East, Asia, Central and Eastern Europe, Latin America IC-SOHO Study (6-month data) Hostile/aggressive behavior outcomes	same as Dossenbach 2004	same as Dossenbach 2004
Bond, 2004 United States	9 months	Olanzapine 12.9 mg Risperidone 5.4 mg
Brown, 2005 United States	NR	Ziprasidone Olanzapine

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Barner, 2004 United States	Included subjects aged 18+ who had not received a typical AP or AAP 6 months prior to the dispensing of a typical AP or AAP, and had not been diagnosed with DM or used an antidiabetic drug 12 months before being prescribed a typical AP or AAP.	Mean age 59.4 94.3% male 69.9% white	6735 3469 3469	NR NR 3469
Bitter, 2005 Africa, the Middle East, Asia, Central and Eastern Europe, Latin America IC-SOHO Study (6-month data) Hostile/aggressive behavior outcomes	Subset of patients who sustained monotherapy and had hostile/aggressive outcome data available at 3- and 6-months	Mean age=35.2 years 54% male Ethnicity NR	7655/5828/3135	NR/NR/3135
Bond, 2004 United States	Schizophrenia or schizoaffective disorder	Mean age=40.8 years 59% male 45% Caucasian; 42% Africa American; 3% other	551/124/90	NR/NR/90
Brown, 2005 United States	Schizophrenia or other psychoses	Mean age (years): Ziprasidone=47.3; Olanzapine=53.9 Gender: Ziprasidone=90.9% male; Olanzapine=96.1% male Ethnicity: NR	NR/NR/191	NR/NR/191

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Barner, 2004 United States	NR
Bitter, 2005 Africa, the Middle East, Asia, Central and Eastern Europe, Latin America IC-SOHO Study (6-month data) Hostile/aggressive behavior outcomes	Change in proportions of patients with hostile/aggressive behavior from baseline to 6 months: Clozapine: -16.8% Olanzapine: -23.1% Quetiapine: -18.3% Risperidone: -22.7% Odds ratios for improvement of hostility over time (95% CI): Risperidone vs clozapine: 1.83 (1.05, 3.20) Olanzapine vs clozapine: 1.67 (1.01, 2.75)
Bond, 2004 United States	work outcomes: olanzapine (n=39) vs risperidone (n=27) vs first-generation anti-psychotics (n=24) paid employment at any time; 29(74%) vs 17(63%) vs 13(54%), NS integrated employment at any time: 16(41%) vs 8(30%) vs 8(33%), NS second generation vs first generation: vocational activities: 76% vs 50%, p<0.05 increase in vocational activities: higher vs lower, p<0.001 monthly rate of paid employment: higher vs lower, NS monthly rate of integrated employment: greater vs lower, p=0.001
Brown, 2005 United States	Weight changes Patients gained an average of 3.9kg on olanzapine (P<0.001) Patients lost on average 1.5kg on ziprasidone (P>0.05) Patients switched from olanzapine to ziprasidone lost an average of 3.4kg over the course of therapy (P=0.002) Metabolic changes Olanzapine was associated with an 8% increase in total cholesterol (P=0.01), an 11% increase in LDL, a 4% decrease in HDL, a 27% increase in triglycerides (P=0.05) and a 6% increase in HbA1c (P<0.05) Ziprasidone was associated with a 7% reduction in total cholesterol, a 14% decrease in LDL, an 8% increase in HDL, a 7% decrease in triglycerides and a 9.4% reduction in HbA1c

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Barner, 2004 United States	Frequency of new-onset diabetes mellitus among patients taking AAPs: AAP group (n=2477) 7.2% (ns) Typical AP group (n=992) 7.0% (ns) Risperidone 7.5% (ns) Quetiapine 5.8% (ns) Olanzapine 6.4% (ns) Adjusted OR of new-onset diabetes mellitus (95% CI): Olanzapine 0.976 (0.594-1.605) Quetiapine 1.149 (0.531-2.485) Risperidone 0.926 (0.544-1.579)	Dose and duration of treatment are not controlled for in this analysis
Bitter, 2005 Africa, the Middle East, Asia, Central and Eastern Europe, Latin America IC-SOHO Study (6-month data) Hostile/aggressive behavior outcomes	NR	
Bond, 2004 United States	NR	
Brown, 2005 United States	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Buse, 2003 United States	AdvancePCS Inc	Retrospective	≥2 years
Caro, 2002 Quebec	Database: Regie de l'Assurance Maladie du Quebec	Retrospective	1/1/97 to 12/31/99
Castro 2007 Brazil	Chart review: Institute of Psychiatry, Universidade de Sao Paulo	Retrospective	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Buse, 2003 United States	NR	Clozapine: 183.1 mg/day Olanzapine: 5.1 mg/day Quetiapine: 79.9 mg/day Risperidone: 1.2 mg/day Haloperidol: 2.5 mg/day Thioridazine: 43.9 mg/day
Caro, 2002 Quebec	NR	Olanzapine Risperidone
Castro 2007 Brazil	12/1/97-12/31/99	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Buse, 2003 United States	Schizophrenia	Mean age: 52 years 63% male	5,816,473 58,751 58,751	Withdrawn=N/A (retrospective) Lost to follow-up=N/A (retrospective) Analyzed=58,751
Caro, 2002 Quebec	Psychotic disorders ≥ 1 prescription for olanzapine or risperidone	Mean age NR 47.2% male Race NR	NR 34,692 33,946 Olanzapine=19,153 Risperidone=14,793	NR NR 33,946
Castro 2007 Brazil	Patients with schizophrenia who were discharged on a regimen of either haloperidol, risperidone or clozapine Exclusion criteria: patients discharged on two or more antipsychotics, patients with another axis 1 disorder and diagnosis of neurological disorders	Haloperidol/Risperidone/Clozapine Mean age: 38.28±10.17/37.59±11.72/35.55±9.48 Male (n): 17/10/21 Ethnicity: NR	NR NR 96 (43 haloperidol, 22 risperidone, 31 clozapine)	NR NR 96

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Buse, 2003 United States	Risk of Diabetes Mellitus: olanzapine: P=0.479 clozapine: P=0.496 quetiapine: P=0.033 haloperidol: P=0.040
Caro, 2002 Quebec	NR
Castro 2007 Brazil	Haloperidol/Risperidone/Clozapine Mean time to hospital readmission (d): 395±318 (range 54-1015)/284±200 (range 6-596)/264±157 (range 88-427) Median time to hospital readmission (d):286/271/303 *No significant difference in time to rehospitalization between groups (ANOVA F=0.66; df=2; p=0.53) Mean length of follow-up for patients who were not readmitted (d): 718±483 (range 14-1095)/879±421 (range 22-1095)/1053±210 (range 26-1095) Percentage of patients remaining non-hospitalized: 12 months: 84/73/90 24 months: 79/59/84 36 months: 74/59/84 Rehospitalization rates (%): 12 months: 16/27/10 24 months: 21/41/16 36 months: 26/41/16 *No significant difference in rehospitalization rates between treatment groups; P-value=NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Buse, 2003 United States	Hazard ratio of developing diabetes comparing antipsychotics to haloperidol group: olanzapine: risperidone: P=0.479 quetiapine: P=0.040 clozapine: P=0.496	
Caro, 2002 Quebec	Diabetes Olanzapine=319/17 Risperidone=217/16 p=0.43 (Cases/rate per 1000 patient years)	
Castro 2007 Brazil	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Citrome 2004 US (New York State)	Integrated Research Database, containing patient information and drug prescription information for every inpatient within the 17 adult civil facilities of the NY State psychiatric hospital system	Retrospective	January 1, 2000-December 31, 2002
Conley, 1999 United States	Record review: Maryland state psychiatric facilities	Prospective	3/14/94 to 12/31/95
Cooper, 2005 Canada	Database: Quebec health insurance database and Quebec database for hospitalizations	Retrospective	July 1, 1996 through August 31, 2006
Cooper, 2007 Canada	Database: Quebec health insurance board and Quebec registry of hospitalizations	Retrospective	January 1, 1997 to August 31, 1999

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Citrome 2004 US (New York State)	Case group: mean 121 ± 60.9 days Control group: mean 133 + 55 days	clozapine risperidone olanzapine quetiapine Mean doses not reported
Conley, 1999 United States	NR	Clozapine Risperidone
Cooper, 2005 Canada	1 year	Olanzapine Risperidone
Cooper, 2007 Canada	1 year	Low intensity: Olanzapine= ≤9.7mg/day; Risperidone= ≤1.9mg/day; Clozapine= ≤300mg/day; Quetiapine= ≤100mg/day Medium intensity: Olanzapine= >9.7mg/day but ≤10.0mg/day; Risperidone= >1.9mg/day but ≤4.0mg/day; Clozapine= >300mg/day but ≤425mg/day; Quetiapine= >100mg/day but ≤300mg/day High intensity Olanzapine= >10mg/day; Risperidone= >4mg/day; Clozapine= >425mg/day; Quetiapine= >300mg/day

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Citrome 2004 US (New York State)	Case group: those who received new prescription of antidiabetic medication. Required to have at least a 30-day period of hospitalization before the start of the prescription. Control group: Those who did not receive a prescription of antidiabetic medication, matched to those in case group on calendar year,then length of stay, then race, then age group, then diagnosis.	Case group: Mean age 43.3 years (SD 11.4) 61% male 32% white Control group: Mean age 43.7 years (SD 12.8) 71% male 32% white	13,611 8,461 1,629	NR NR 1,629
Conley, 1999 United States	Schizophrenia	Mean age=40.4 60.5% male Race NR	NR NR 124 (clozapine=49, risperidone=75)	NR NR unclear
Cooper, 2005 Canada	Schizophrenia	Age: 8% 0-24 years; 50% 25-44 years; 32% 45-64 years; 10% 65 years and over Gender: 57% male	38,048/6,405/6,405	NR/NR/6,405
Cooper, 2007 Canada	Schizophrenia	Age: 27% 0-34 years; 63% 35-64 years; 10% 65 years or older Gender: 57% male Ethnicity: NR	NR/NR/6662	NR/NR/6662

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Citrome 2004 US (New York State)	
Conley, 1999 United States	NR
Cooper, 2005 Canada	Mean days of use before discontinuation olanzapine=233 risperidone=142 (60.5% of individuals discontinued use of initial treatment prior to one-year) Concomitant use Of those who stayed on their initial treatment for at least one year: 738 (47.3%) of olanzapine users and 435 (48.5%) of risperidone users received at least one concomitant antipsychotic prescription during treatment
Cooper, 2007 Canada	Persistence Individuals started on clozapine were more likely to be persistent than those on olanzapine, however those on olanzapine were more likely to be persistent than those on risperidone Individuals who received a dosage in the low or medium intensity were more likely to be persistent than those receiving the high intensity dosage

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Citrome 2004 US (New York State)	Adjusted odds ratio (95% CI) for development of diabetes vs typical antipsychotic use: Clozapine only: 2.06 (1.07, 3.99) Olanzapoine only: 1.57 (0.87, 2.82) Quetiapine only: 3.09 (1.59, 6.03) Risperidone only: 1.50 (0.81, 2.79) More than one atypical antipsychotic: 2.86 (1.57, 5.20)	
Conley, 1999 United States	Hospitalization Readmission rates (% patients) Year 1=13% vs 17%; p=NS Year 2=13% vs 34%; p=NS Mean time to readmission (days)=360 vs 319	
Cooper, 2005 Canada	NR	
Cooper, 2007 Canada	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Coulter, 2001 International	Database: Uppsala Monitoring Centre in Sweden	Unclear	NR
de Haan, 1999 Netherlands	University of Amsterdam	Retrospective	7.3 months average
de Haan, 2002 Netherlands	Academic Medical Center, University of Amsterdam	Prospective	6 weeks
de Leon, 2004 United States	Clinical Research Center, Norristown State Hospital, Norristown	Retrospective	16 weeks
Dinakar, 2002 United States	Rockland Psychiatric Center, NY	Retrospective	3 months
Dolder, 2002 United States	Database: VA San Diego Healthcare System	Retrospective	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Coulter, 2001 International	NR	Clozapine Olanzapine Quetiapine Risperidone
de Haan, 1999 Netherlands	NR	clozapine: NR other drugs: NR
de Haan, 2002 Netherlands	NR	Olanzapine(N=39): 14.2mg Risperidone(N=23): 4.1mg
de Leon, 2004 United States	NR	All patients switched from 4 weeks on 10 mg/day of haloperidol, to 100, 300, 600 mg/day clozapine
Dinakar, 2002 United States	NR	At endpoint: olanzapine: 52.75 risperidone: 52.53
Dolder, 2002 United States	12 months	Haloperidol 8mg/day Perphenazine 12mg/day Risperidone 4mg/day Olanzapine 12.5mg/day Quetiapine 400mg/day

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Coulter, 2001 International	NR	NR NR NR	NR NR NR	NR NR Reports analyzed: Clozapine=24730, Olanzapine=6,135, Quetiapine=709, Risperidone=10,746
de Haan, 1999 Netherlands	Schizophrenia or schizoaffective disorder, schizophreniform disorder	Mean age: 20.9 years	NR/NR/121	Withdrawn=N/A (retrospective) Withdrawn=N/A (retrospective) Analyzed=121
de Haan, 2002 Netherlands	N=113 Schizophrenia, 15% OCD disorder, drug class naïve	Mean age: 22.4 years	NR/113/113	NR/NR/62
de Leon, 2004 United States	Schizophrenia	Mean age: 45.5 years 54% Male 85.5% Caucasian 14.5% African-American	NR/NR/40	NR/NR/35
Dinakar, 2002 United States	Schizophrenia	Mean age: 55.5 years Gender and Ethnicity NR	NR/79/79	0/0/79
Dolder, 2002 United States	Schizophrenia, schizoaffective disorder, mood disorder with psychotic features, or psychosis not otherwise specified	Age=49.7 89.9% male Ethnicity (%) Caucasian=61.8 African American=18.4 Hispanic=9.4 Other=5.5	629/NR/288	Withdrawn=N/A (retrospective) Withdrawn=N/A (retrospective) Analyzed=288

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Coulter, 2001 International	NR
de Haan, 1999 Netherlands	% of patients experiencing an emergence of increase of obsessions after treatment: C: 20.6% vs other drugs: 1.3%; (P<.01)
de Haan, 2002 Netherlands	Yale-Brown Obsessive Compulsive Scale (YBOCS) Mean Scores: At Admission: R: 2.4 vs O: 2.4 At Endpoint (6 weeks): R: 2.2 vs O: 1.9
de Leon, 2004 United States	NR
Dinakar, 2002 United States	BPRS scores: baseline vs endpoint O: 67.03 vs 52.75 R: 62.70 vs 52.53
Dolder, 2002 United States	Adherence Rates-cumulative mean gap ratio Those treated with atypical antipsychotics had significantly smaller gaps in therapy compared to those treated with typical antipsychotics at 6-months (p=0.001) and at 12-months (p=0.001). Olanzapine had a significantly lower gap ratio compared to haloperidol at 6-months (p=0.008), no other significant differences between individual medications was observed at either 6-months or 12-months. Adherence Rates-compliant fill rate Those treated with atypical antipsychotics had significantly higher adherence rates at 6-months compared to those treated with typical antipsychotics (p=0.05), at 12-months the trend was similar, though not at the significant level.

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Coulter, 2001 International	Cardiomyopathy or myocarditis (# cases/%) Clozapine=231/0.9% Olanzapine=8/0.1% Quetiapine=2/0.3% Risperidone=16/0.1%	
de Haan, 1999 Netherlands	NR	
de Haan, 2002 Netherlands	NR	
de Leon, 2004 United States	Within-subject correlation of prolactin levels: C: 0.32 vs H: 0.75	
Dinakar, 2002 United States	NR	
Dolder, 2002 United States	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Dossenbach et al, 2004 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (6 month data)	Prospectively collected, multicenter study data	Prospective	6 mos (interim data - planned exposure 3 yrs)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Dossenbach et al, 2004 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (6 month data)	NR	Mean doses at 6 mos: olanzapine 10.9 mg/day (SD 4.8) quetiapine 339.5 mg/day (SD 188.9) risperidone 4.0 mg/day (SD 2.1) haloperidol 12.2 mg/day (SD 9.3)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Dossenbach et al, 2004 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (6 month data)	Schizophrenia	Mean age 35.5 yrs (SD 12.2) 54% male Ethnicity NR	7658/NR/5833	NR/NR/unclear; according to the text "as a result of missing data, the number of patients in each subgroup may differ for each comparison"

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Dossenbach et al, 2004 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (6 month data)	CGI-Severity of Illness Scale score, mean change from baseline at 6 months: Overall: O -1.44 (SE 0.04) v Q -1.02 (SE 0.09) v R -1.24 (SE 0.05) v H -0.87 (SE 0.08) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R, & H; R v H Positive: O -1.44 (SE 0.05) v Q -1.01 (SE 0.10) v R -1.27 (SE 0.06) v H -1.07 (SE 0.09) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R, & H Negative: O-1.21 (SE 0.04) v Q -0.82 (SE 0.09) v R -0.98 (SE 0.05) v H -0.65 (SE 0.08) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R & H; R v H Depressive: O -1.11 (SE 0.04) v Q -0.83 (SE 0.09) v R -0.91 (SE 0.05) v H -0.67 (SE 0.08) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R & H Cognitive: O -1.05 (SE 0.04) v Q -0.61 (SE 0.09) v R -0.83 (SE 0.05) v H -0.54 (SE 0.08) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R & H; R v H

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Dossenbach et al, 2004 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (6 month data)	Weight change: significantly higher with olanzapine use compared to all other interventions (p<0.0001) O 2.57 kg (SE 0.21) Q 0.58 kg (SE 0.44) R 1.49 kg (SE 0.26) H 0.73 (SE 0.40)	Data on pts remaining on monotherapy or switching therapies not abstracted

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Dossenbach et al, 2005 Dossenbach 2006 for sexual dysfunction results 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (12 month data)	Same as Dossenbach 2004	Same as Dossenbach 2004	12 months

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Dossenbach et al, 2005 Dossenbach 2006 for sexual dysfunction results 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (12 month data)	NR	Same as Dossenbach 2004

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Dossenbach et al, 2005 Dossenbach 2006 for sexual dysfunction results 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (12 month data)	Schizophrenia	same as Dossenbach 2004	same as Dossenbach 2004	1007/225/3551 (from Figure 1 in text)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Dossenbach et al, 2005 Dossenbach 2006 for sexual dysfunction results 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (12 month data)	CGI-Severity of Illness Scale score, least squares mean change from baseline at 12 months: Overall: O -1.80 (SE 0.04) v Q -1.62 (SE 0.06) v R -1.39 (SE 0.11) v H -1.04 (SE 0.11) Statistically significant difference (p≤0.001) for the following comparisons: O v Q, R, & H; R v H Positive: O -1.74 (SE 0.05) v Q -1.64 (SE 0.06) v R -1.44 (SE 0.12) v H -1.16 (SE 0.11) Statistically significant difference (p≤0.001) for the following comparisons: O v H; R v H Negative: O -1.58 (SE 0.05) v Q -1.38 (SE 0.06) v R -1.25 (SE 0.12) v H -0.88 (SE 0.11) Statistically significant difference (p≤0.001) for the following comparisons: O v R & H; R v H Depressive: O -1.38 (SE 0.05) v Q -1.21 (SE 0.06) v R -1.06 (SE 0.12) v H -0.73 (SE 0.11) Statistically significant difference (p≤0.001) for the following comparisons: O v R & H; R v H Cognitive: O -1.34 (SE 0.05) v Q -1.17 (SE 0.06) v R -1.05 (SE 0.12) v H -0.64 (SE 0.11) Statistically significant difference (p≤0.001) for the following comparisons: O v R & H; R v H Relapse rates at 12 months among previous responders: O 7.7% v R 9.0% (OR 1.07 [0.68-1.68] vs olanzapine) v Q 12.5% (OR 1.76 [0.66-4.74] vs olanzapine) v H 30.0% (OR 6.57 [3.10-13.93] vs olanzapine) Proportion of patients who had worsened at 12 months: O 20.2% v R 24.8% (OR 1.29 [1.04-1.59] vs olanzapine) v Q 37.0% (OR 2.28 [1.47-3.54] vs olanzapine) v H 37.1% (OR 2.37 [1.60-3.52] vs olanzapine)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Dossenbach et al, 2005 Dossenbach 2006 for sexual dysfunction results 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (12 month data)	Weight gain, least squares mean: O 3.4kg (CI 2.9-4.0); p<0.001 v R; R 2.2kg (CI 1.5-3.0); Q 1.9kg (CI 0.5-3.3); H 2.2kg (CI 0.9-3.4) Patients with weight gain >7% of baseline: O 760/1963 (39%) v R 153/549 (28%) v Q 20/80 (25%) v H 27/105 (26%) Relapse months 3-12, based on subset of initial responders (total n=1682): O 99/1292 (7.7%) R 28/310 (9.0%); OR 1.07 (0.68-1.68) vs olanzapine Q 5/40 (12.5%); OR 1.76 (0.66-4.74) vs olanzapine H 12/40 (30.0%); OR 6.57 (3.10-13.93) vs olanzapine p<0.001: O v H; R v H Compliance (based on patient perception): O 1637/1916 (85.4%) v R 445/547 (81.4%) v Q 61/84 (72.6%) v H 72/121 (59.5%) p<0.001: O v H; R v H Sexual dysfunction-related AE's during 12-month treatment period for olanzapine vs risperidone vs quetiapine vs haloperidol/odds ratio (95% CI) for comparison to olanzapine Patient perception of sexual dysfunction: 55.7% vs 67.8% (OR 2.02, 95% CI 1.63, 2.49) vs 60.2% (OR 0.88, 95% CI 0.56, 1.39) vs 71.1% (OR 2.47, 95% CI 1.61, 3.77) Loss of libido: 46.4% vs 60% (OR 2.05, 95% CI 1.67, 2.52) vs 54.6% (OR 1.16, 95% CI 0.72, 1.85) vs 68.1% (OR 3.25, 95% CI 2.14, 4.92) Impotence/sexual dysfunction: 32% vs 46% (OR 2.17, 95% CI 1.72, 2.73) vs 43% (OR 1.26, 95% CI 0.74, 2.14) vs 52.3% (OR 3.04, 95% CI 1.94, 4.74) Amenorrhea/menstrual disturbances: 29.5% vs 42.1% (OR 2.26, 95% CI 1.63, 3.15) vs 20.9% (OR 0.46; 95% CI 0.20, 1.05) vs 53.8% (OR 4.06, 95% CI 2.20, 7.51)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Dossenbach 2008 IC-SOHO study (36 month data)	Dossenbach 2004	Same as Dossenbach 2004	36 months

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Dossenbach 2008 IC-SOHO study (36 month data)	NR	Same as Dossenbach 2004

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Dossenbach 2008 IC-SOHO study (36 month data)	Schizophrenia	same as Dossenbach 2004	Same as Dossenbach 2004	2293/NR/3835

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Dossenbach 2008 IC-SOHO study (36 month data)	Olanzapine vs risperidone vs quetiapine % responding to treatment at 36 months 78% vs 65% vs 47% Median time to response (95% CI) mo: 5.2 (5.0 to 5.5) vs 6.3 (6.0 to 6.7) vs 11.3 (6.3 to 17.5) Olanzapine as a reference HR (95% CI): vs risperidone 0.8 (0.7 to 0.8), p<0.001, Number needed to treat (95% CI) at 36 mo 15 (10-31) HR (95% CI): vs quetiapine 0.6 (0.4 to 0.7), p<0.001, nmber needed to treat (95% CI) at 36 mo 8 (4 to 50) Risperidone as a reference HR (95% CI): vs quetiapine 0.8 (0.6 to 1.0), p=0.037, Number needed to treat (95% CI) at 36 mo 12 (5 to -23) % patients relapsed following treatment response: 12% vs 14% vs 18%

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Dossenbach 2008 IC-SOHO study (36 month data)	EPS Olanzapine as reference Adjusted OR (95% CI) vs Risperidone 5.63 (4.27 to 7.40), p<0.001, Number needed to treat (95% CI)at 36 mo 5 (5 to 7) Adjusted OR (95% CI) vs Quetiapine 0.23 (0.07 to 0.75), p=0.015, Number needed to treat(95% CI at 36 mo -18 (-57 to -11) Risperidone as a reference Adjusted OR (95% CI) vs Qutiapine: 0.04 (0.01 to 0.13), p<0.001, Number needed to treat (95% CI) at 36 mo -4 (-5 to -4) Tardive dyskinesia Olanzapine as reference Adjusted OR (95% CI) vs Risperidone: 4.15 (2.37 to 7.27), p<0.001, Number needed to treat at 36 mo 42 (26 to 105) Adjusted OR (95% CI) vs Quetiapine : 1.37 (0.39 to 4.72), p=0.623, Number needed to treat at 36 mo 138 (30 to -53) Risperidone as a reference Adjusted OR (95% CI vs Quetiapine: 0.33 (0.09 to 1.16), p=0.084, Number needed to treat at 36 mo -59 (81 to -22) Sexual dysfunction: Olanzapine as a reference Adjusted OR (95% CI) vs Risperidone 2.14 (1.70 to 2.70), p<0.001, Number needed to treat (95% CI) at 36 mo 10 (7 to 22) Adjusted OR (95% CI) vs Quetiapine 1.43 (0.78 to 2.60), p=0.246, Number needed to treat at 36 mo 39 (7 to -10) Risperidone as a reference Adjusted OR (95% CI) vs Quetiapine 0.67 (0.36 to 1.23), p=0.196, Number needed ot treat at 36 mo -14 (17 to -5) Weight gain>7% from baseline Olanzapine as reference Adjusted OR (95% CI) vs risperidone 0.63 (0.54 to 0.73), p<0.001, number needed to treat (95% CI) at 36 mo -9 (48 to -4) Quetiapine as reference Adjusted OR (95% CI) vs quetiapine 0.81 (0.55 to 1.21), p=3.00, number needed to treat at 36 mo (95% CI) -18 (12 to -5)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Etminan, 2003 Ontario	Database: Ontario Drug Benefit (ODB) claims database	Unclear	NR
Feldman, 2004 United States	AdvancePCS Inc	Retrospective	6-9 months
Fuller, 2003 Ohio	Database: Veteran's Integrated Service Network 10	Retrospective	1/1/97 to 12/31/00
Ganguli, 2001 United States	Multiple sources	Retrospective	4 months

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Etminan, 2003 Ontario	NR	Olanzapine Quetiapine Risperidone
Feldman, 2004 United States	NR	NR
Fuller, 2003 Ohio	NR	Risperidone 2.8 mg Olanzapine 10.0 mg Fluphenazine 12.2 mg Haloperidol 8.4 mg
Ganguli, 2001 United States	NR	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Etminan, 2003 Ontario	Schizophrenia	Mean age=84.2 34.2% male Race NR	NR NR 3250	NR NR 2984 (individual group n's NR)
Feldman, 2004 United States	Geriatric	Mean age: 79.2 years 60.8% female Ethnicity NR	NR/NR/1,836,799	NR/NR/30,953
Fuller, 2003 Ohio	Range of psychiatric diagnoses: Schizophrenia=61% Depression=47% Bipolar Disorder=26% Dementia=8%	Mean age=53 Gender NR 73% White	NR NR 5837	NR NR 5837
Ganguli, 2001 United States	Schizophrenia	Mean age: 41.3 years 56.5 Males Caucasian: 57% African-American:38% Other: 5%	NR/NR/100	0/0/100

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Etminan, 2003 Ontario	NR
Feldman, 2004 United States	Development of Diabetes Mellitus (Risk Ratio): All combined conventional antipsychotics: 3.2; P<0.001 All combined atypicals: 3.3; P<0.001 clozapine: 5.8; P=0.002 olanzapine: 3.5; P<0.001 quetiapine: 2.5; P<0.001 risperidone: 3.4; P<0.001
Fuller, 2003 Ohio	NR
Ganguli, 2001 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Etminan, 2003 Ontario	Diabetes Diabetic events (% patients): Olanzapine=2.1 Quetiapine=1.0 risperidone 2.1	Age - older adults
Feldman, 2004 United States	NR	
Fuller, 2003 Ohio	Risk (Hazard Ratio, 95% CI) of developing diabetes for olanzapine vs risperidone: Univariate analysis=HR 1.29, 95% CI 1.00 to 1.67; Multivariate analysis=HR 1.37, 95% CI 1.06 to 1.76	
Ganguli, 2001 United States	Change in Mean Body Weight/BMI at Endpoint: Weight: risperidone: 82.8kg, P=NS olanzapine: BMI: risperidone: olanzapine:	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Garcia-Cabeza, 2003 Montes, 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Multicenter Controlled	See above	See above
Gasquet, 2005 Europe (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK) SOHO (secondary publication)	Prospectively collected, multicenter study data	Prospective	6 mo (interim analysis of planned 3-yr term)
Gianfrancesco, 2006a United States	Database: PharMetrics	Retrospective	January 1999 through August 2003

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Garcia-Cabeza, 2003 Montes, 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	NR	Overall mean dose: Olanzapine: 13 mg/d Risperidone: 5.4 mg/d Haloperidol: 13.6 mg/d
Gasquet, 2005 Europe (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK) SOHO (secondary publication)	NR	Olanzapine 11.1 mg/day (SD 5.0) Risperidone 4.6 mg/day (SD 2.6)
Gianfrancesco, 2006a United States	NR	Atypical Antipsychotics Risperidone: 3.0mg/day Olanzapine: 11.4mg/day Quetiapine: 264mg/day Ziprasidone: 86mg/day Typical Antipsychotics Haloperidol: 10.5mg/day Perphenazine: 13.5mg/day Thioridazine: 128mg/day Thiothixene: 11.2mg/day

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Garcia-Cabeza, 2003 Montes, 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Paranoid schizophrenia: 65.1% Undifferentiated schizophrenia: 13.5% Residual schizophrenia: 12.3% Subjective response and compliance with antipsychotic treatment using 10 Item Drug Attitude Inventory (DAI-10)	Mean age: 35.4 63.9% male Ethnicity NR	NR/ 2967/ 2657	unclear; unclear; 2348 for safety at 6 months and 2189 for DAI-10 score at 6 months
Gasquet, 2005 Europe (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK) SOHO (secondary publication)	Previously untreated schizophrenics	Mean age 33.6 yrs 60% male Ethnicity NR	1033/NR/919	134/NR/919
Gianfrancesco, 2006a United States	Schizophrenia or schizoaffective disorder	Mean age (years): 41.5 % male: 48.9	NR/NR/5683	NR/NR/5683

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Garcia-Cabeza, 2003 Montes, 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	From Montes 2003: Mean changes in scale scores for olanzapine vs risperidone vs conventional antipsychotics (p-value is NS unless otherwise specified and represents comparison to conventional antipsychotics group) CGI-S: -1.8 vs -2.0 vs -1.5 GAF: 29.2 vs 32.2 vs 22.6 EuroQol-1:0.35 vs 0.36 vs 0.25 Visual Analogue Scale (0=worst state of health possible to 100=best state of health possible): 26 (p<0.05) vs 28 (p<0.05) vs 17.5 AWAD scale (subjective attitude towards medication; positive score=positive subjective response, negative score=negative response): 4.7 vs 3.1 vs 1.3
Gasquet, 2005 Europe (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK) SOHO (secondary publication)	EQ-5D VAS at 6 months: O 64.4 (SD 18.1) v R 61.1 (SD 18.8); adjusted mean difference O v R: -3.73 (CI -1.48 to -5.97); p=0.001
Gianfrancesco, 2006a United States	Comparisons of treatment duration Treatment duration for risperidone, olanzapine, and ziprasidone were not significantly different from the typical antipsychotics, but quetiapine demonstrated a nonsignificant trend for shorter treatment durations compared with the combined group of typical agents (P=0.091). Quetiapine had significantly shorter treatment durations than risperidone (P=0.024) and olanzapine (P=0.004). Differences between other atypical agents were not significant. Patient characteristics with significant increasing associations with treatment duration included age, switch from another antipsychotic, substance dependence/abuse, more versus less managed form of coverage, and earlier date for start of treatment episode (all P<0.05).

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Garcia-Cabeza, 2003 Montes, 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Subjective Response : Mean DAI-10 Score (range: -10 to +10) , baseline vs 6 months: olanzapine: +0.17 vs +4.63 risperidone: +0.32 vs +3.42, p<0.001 vs Olz haloperidol: -1.25 vs +1.68, p <0.001 vs Olz and p=0.003 vs Ris Compliance with principal antipsychotic treatment, % of pts at each level *data given as Olz vs Ris vs Hal* High compliance: 84.8% vs 74.2% vs 69.8% (p=0.001 for Olz vs Ris) Moderate compliance: 11.1% vs 19.4% vs 27.1% (p=0.022 for Olz vs Hal) Low compliance: 2.5 % vs 5% vs 2.1% Nil: 1.6% vs 1.4% vs 1% % of pts with EPS, baseline vs 6 month data, p=NR: Olz: 35.8% vs 31.9% Ris: 48.3% vs 44.6% Hal: 69.2% vs 66.3%	
Gasquet, 2005 Europe (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK) SOHO (secondary publication)	Weight gain at 6 months: O 3.1kg (SD 4.9) v R 2.1 (SD 4.6); adjusted mean difference O v R: -1.0 (CI -1.8 v -0.1)	
Gianfrancesco, 2006a United States	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Gianfrancesco, 2006b United States	Medical and prescription claims data for commercially insured patients	Retrospective	1999 to August 2003
Gianfrancesco, 2002 United States	Database: Two mixed indemnity and managed care health plans located in the northeastern and southeastern United States (unspecified)	Retrospective	January 1996 through December 1997
Gianfrancesco, 2003a United States	Database: Blue Cross/Blue Shield claims database	Retrospective	April 1997 through October 2000

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Gianfrancesco, 2006b United States	Unclear	Risperidone, olanzapine, quetiapine, ziprasidone mean dosages NR
Gianfrancesco, 2002 United States	Risperidone=6.8 months Olanzapine=6.1 months High-potency conventionals=7 months Low-potency conventionals=7.1 months Clozapine=9.4 months	Mean dosages in form of risperidone equivalents: Risperidone=2.3 mg Olanzapine=3.6 mg High-potency conventionals=1.7 mg Low-potency conventionals=1.7 mg Clozapine=2.5 mg
Gianfrancesco, 2003a United States	Risperidone=9.1 months Olanzapine=8.7 months Quetiapine=7.1 months Conventionals=12.1 months	Risperidone Olanzapine Quetiapine Conventionals Mean doses NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Gianfrancesco, 2006b United States	Schizophrenia	Mean age=42 43% male Ethnicity NR	NR/NR/3807	NR/NR/3807
Gianfrancesco, 2002 United States	Psychosis diagnosis (schizophrenia, bipolar and manic, major depressive, dementia, other psychoses)	Untreated vs treated (restricted to those WITHOUT Type 2 Diabetes at 4 months prior to observation) Mean age=41.9 vs 45.3 % male=40.4% vs 36.6% Race nr	NR NR NR	NR NR NR
Gianfrancesco, 2003a United States	Schizophrenia=14% Bipolar and manic=35%, Major depressive=38%, Other psychoses=13%	Mean age=37.5 41% male Race NR	NR NR 6582 patients Treatment episodes: Risperidone=2860, Olanzapine=2703, Quetiapine=922, Conventional antipsychotics=2756	NR NR Analyzed=6582 patients (Treatment episodes: Risperidone=2860, Olanzapine=2703, Quetiapine=922, Conventional antipsychotics=2756)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Gianfrancesco, 2006b United States	Hazard ratios (95% CI) for risk of hospitalization Olanzapine vs risperidone=1.34 (1.03, 1.74) Risperidone vs quetiapine=1.05 (0.71, 1.55) Risperidone vs ziprasidone=1.14 (0.55, 2.37) Olanzapine vs quetiapine=1.40 (0.94, 2.07) Olanzapine vs ziprasidone=1.52 (0.73, 3.15) Ziprasidone vs quetiapine=0.92 (0.42, 2.02)
Gianfrancesco, 2002 United States	NR
Gianfrancesco, 2003a United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Gianfrancesco, 2006b United States	NR	
Gianfrancesco, 2002 United States	Odds Ratio (vs Risperidone) for 12 months of treatment (extrapolated from 1-month treatment rates) (excluded patients with pre-existing Type II Diabetes identified at 8-month screening): Olanzapine=3.53, p<0.05 Clozapine=8.45, p<0.05 Frequency of Type 2 Diabetes after at least 12 months' treatment (excluding patients with pre-existing Type II Diabetes identified at 8-month screening): Risperidone=2/90 (2.2%) Olanzapine=4/56 (7.1%) Clozapine=1/4 (25%)	
Gianfrancesco, 2003a United States	Frequency of Type II Diabetes at 4-8 months/8-12 months/>12 months: Risperidone=0.2/0.0/0.6 Olanzapine=0.2/1.3/3.0 Quetiapine=0.5/1.2/0.9 Conventional=0.0/1.9/1.4 One-month odds ratios (95% CI) converted to 12-months for each drug vs no antipsychotic treatment: Risperidone=0.660 (0.311 to 1.408) Olanzapine=1.426 (1.046 to 1.955) Quetiapine=0.976 (0.422-2.271) Conventionals=1.049 (0.688-1.613)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Gianfrancesco, 2003b United States	Database: Two mixed indemnity and managed care health plans located in the northeastern and southeastern United States (unspecified)	Retrospective	January 1996 through December 1997
Gibson, 2004 United States	Database: Michigan Medicaid administrative claims data set from Michigan's Department of Community Health (MDCH)	Retrospective	January 1996 through September 1997

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Gianfrancesco, 2003b United States	Patients not taking antipsychotics=13.7 months Risperidone=6.1 months Olanzapine=5.4 months High-potency Conventional Antipsychotics=6.5 months Low-potency conventional antipsychotics=6.5 months	(Risperidone equivalents) Risperidone 2.1 mg Olanzapine 3.4 mg High-potency conventional antipsychotics 1.6 mg Low-potency conventional antipsychotics 1.6 mg
Gibson, 2004 United States	1 year	Mean initial dosages: olanzapine 9.9mg risperidone 3.8mg haloperidol 18.2mg

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Gianfrancesco, 2003b United States	% patients NOT taking antipsychotics/% patients TAKING antipsychotics: Bipolar=48.1%/30.6% Major Depressive Disorder=39.7%/664.5% Manic=12.2%/4.9%	Patients NOT taking antipsychotics/Patients TAKING antipsychotics: Mean age=41.8/42.2 % male=38.9%/31.8% Race NR	NR NR 5723	NR 5236 patients (Patients NOT taking antipsychotics=2644; Risperidone=849, Olanzapine=656, High-potency conventional antipsychotics=785, Low-potency antipsychotics=302) (excludes those found to have pre-existing Type II diabetes at the 4-month screening period)
Gibson, 2004 United States	Schizophrenia	Haloperidol/Risperidone/Olanzapine: Mean age=39.7/40.5/40.7 years Women (%)=53/48/53 Ethnicity=NR	3,642/1191/1191	NR/NR/1191

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Gianfrancesco, 2003b United States	NR
Gibson, 2004 United States	Patterns of use changes: individuals increased usage of olanzapine as their only antipsychotic medication from 41% to 46% individuals decreased usage of risperidone as their only antipsychotic medication from 61% to 42% individuals decreased usage of haloperidol as their only antipsychotic medication from 81% to 39% Cost reduction: Olanzapine was associated with $2552 lower total cost than risperidone and $2323 lower costs than haloperidol

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Gianfrancesco, 2003b United States	12-month odds ratios (converted from 1-month estimates) that excludes patients found to have pre-existing Type II diabetes at 8-month screening: Relative to Untreated Risperidone=1.024 (0.351-3.015) Olanzapine=4.289 (2.102-8.827) Olanzapine vs risperidone-4.189, p=0.02958	
Gibson, 2004 United States	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Multicenter Controlled	Schizophrenia patients were included when a change of medication was indicated or a new antipsychotic drug treatment was being initiated for whatever reason. Choice of new drug was made by the treating physician.	6 months
Gupta, 2004 United States	Olean General Hospital at the SUNY Upstate Medical University at Syracuse	Prospective	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Olanzapine 13.01 mg Risperidone 5.39 mg Haloperidol 13.64 mg	NR
Gupta, 2004 United States	10 weeks	Quetiapine 4 weeks 392.5 mg/day

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Death Weight gain	Mean age=35.4 63.6% male Race NR	NR NR 2949	798 (25.7%) withdrawals 506 (17.1%) lost to fu 2949 analyzed
Gupta, 2004 United States	Schizophrenia, schizoaffective disorder, bipolar disorder, psychotic disorder, or major depression with psychotic features.	Mean age =46.6 years 56% male Ethnicity: NR	NR/NR/16	2/2/NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	NR
Gupta, 2004 United States	Positive and Negative Syndrome Scale (PANSS): NS Simpson-Angus-Scale (SAS): NS

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Death Olanzapine: 3 (0.1%) Control group: 1 (0.1%) Suicide Olanzapine: 1 (0.05%) Control group: 1 (0.1%) Weight gain Olanzapine: 146 (6.9%) Risperidone: 8 (1.9%) Haloperidol: 1 (0.9%) Olanzapine vs. risperidone: p<0.001 Olanzapine vs. haloperidol: p=NS	
Gupta, 2004 United States	Mean weight loss=2.25kg, p=0.03 BMI declined to 34.4kg/m2, p=0.065 fasting glucose, lipid profile, hemoglobin A1c, serum triglycerides: NS	Patients switched from olanzapine to quetiapine

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Haro, 2006 SOHO (secondary publication) 3-year effectiveness Europe	Same as Haro 2005	Same as Haro 2005	NR
Haro, 2006 SOHO (secondary publication) 12-month medication maintenance outcomes Europe	Same as Haro 2005	Same as Haro 2005	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Haro, 2006 SOHO (secondary publication) 3-year effectiveness Europe	3 years	Same as Haro 2005
Haro, 2006 SOHO (secondary publication) 12-month medication maintenance outcomes Europe	12 months	Same as Haro 2005

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Haro, 2006 SOHO (secondary publication) 3-year effectiveness Europe	Same as Haro 2005; only patients with none or 1 missing visit	Mean age 39.8 years 56.7% male Ethnicity NR	9857 8072 7728	nr/nr/7728
Haro, 2006 SOHO (secondary publication) 12-month medication maintenance outcomes Europe	Same as Haro 2005	Mean age 40 years 56.9% male Ethnicity NR	8519/NR/7186	NR/NR/7186

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Haro, 2006 SOHO (secondary publication) 3-year effectiveness Europe	Patients maintaining treatment for 36 months Olanzapine 1851, Risperidone 619 , Quetiapine 126, Amisulpride 85, Clozapine 123, Oral typical NR Depot typical NR Patient discontinuing for any reason (%) Olanzapine 36.4, Risperidone 42.7 , Quetiapine 66.1, Amisulpride 50.4, Clozapine 33.8, Oral typical 53.1 Depot typical 50.2 Patient discontinuing for lack of efficacy (%) Olanzapine 18.4, Risperidone 22.7 , Quetiapine 48.3, Amisulpride 28.7, Clozapine 17.8, Oral typical 33.8, Depot typical 31.4 Patient discontinuing for intolerability(%) Olanzapine 6.4, Risperidone 10.1 , Quetiapine 14.2, Amisulpride 13.7, Clozapine 7.2, Oral typical 13.3, Depot typical 9.2
Haro, 2006 SOHO (secondary publication) 12-month medication maintenance outcomes Europe	Medication maintenance at 12 months (% pts): Highest frequencies: Clozapine=79.5% and Olanzapine=77% Lowest frequencies: Quetiapine=51.4% and amisulpride=58.2% Frequencies for other cohorts NR Odds ratios (95% CI) of associated with maintenance compared to olanzapine: Risperidone: 0.72 (0.62, 0.83) Quetiapine: 0.36 (0.29, 0.44) Amisulpride: 0.53 (0.39, 0.71) Clozapine: 1.65 (1.20, 2.28) Oral typical: 0.56 (0.45, 0.70) Depot typical: 0.58 (0.46, 0.75)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Haro, 2006 SOHO (secondary publication) 3-year effectiveness Europe	Hospitalization for exacerbation of schizophrenia Hazard ratio (95% CI) Olanzapine 1 Risperidone 1.04 (0.88, 1.23) Quetiapine 1.64 (1.31, 2.05) *** Amisulpride 1.39 (1.01, 1.92) * Clozapine 1.13 (0.83, 1.53) Oral typicals 1.39 (1.08, 1.79) ** Depot typicals 1.44 (1.10, 1.88) ** Suicide attempt % Olanzapine 2.1, Risperidone 1.9 , Quetiapine 1.4, Amisulpride 3.1, Clozapine , Oral typical 0.4, Depot typical 3.5 EPS % Olanzapine 14.7, Risperidone 32.2 , Quetiapine 13.4, Amisulpride 16.8, Clozapine 17.2, Oral typical 31.4, Depot typical 42.8 Tardive dyskinesia % Olanzapine 5.9, Risperidone7.8 , Quetiapine 6.0, Amisulpride 9.8, Clozapine 6.2, Oral typical 8.7, Depot typical 12.9 Loss of libido/impotence Olanzapine 46.9, Risperidone 52.2 , Quetiapine 39.8, Amisulpride 49.2, Clozapine 48.5, Oral typical 50.7, Depot typical 49.7 Gynecomastia, galactorrhea, amenorrhea Olanzapine 11.5, Risperidone 16.7 , Quetiapine 12.4, Amisulpride 18.0, Clozapine 16.4, Oral typical 14.9, Depot typical 13.8 Mean (SD) weight change (kg) Olanzapine 3.6(8.9), Risperidone 2.5(8.5) , Quetiapine 0.6(7.9), Amisulpride 0.5(10.8), Clozapine 3.0(11.5), Oral typical 1.5(6.3), Depot typical 2.6(10.3) * $p \leq 0.05$. ** $p \leq 0.01$. *** $p \leq 0.001$.	
Haro, 2006 SOHO (secondary publication) 12-month medication maintenance outcomes Europe	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Haro, 2006 SOHO (secondary publication) 3-year remission/relapse outcomes Europe	Same as Haro 2005	Same as Haro 2005	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Haro, 2006 SOHO (secondary publication) 3-year remission/relapse outcomes Europe	3 years	Same as Haro 2005

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Haro, 2006 SOHO (secondary publication) 3-year remission/relapse outcomes Europe	Same as Haro 2005; only patients with none or 1 missing visit	Mean age 40.2 years 57.6% male Ethnicity NR	10,218/7112/6516	NR/NR/6516

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Haro, 2006 SOHO (secondary publication) 3-year remission/relapse outcomes Europe	Remission=Scores of 3 or below on the CGI overall severity, positive symptoms score, negative symptoms score, AND cognitive symptoms score Odds ratios (95% CI) of remission compared to olanzapine: Amisulpride: 0.72 (0.56, 0.94) Clozapine: 0.78 (0.65, 0.95) Depot typical: 0.59 (0.50, 0.69) Oral typical: 0.64 (0.55, 0.74) Quetiapine: 0.65 (0.56, 0.76) Risperidone: 0.74 (0.66, 0.83) Odds ratios (95% CI) of relapse compared to olanzapine: Amisulpride: 1.37 (0.99, 1.90) Clozapine: 1.09 (0.78, 1.53) Depot typical: 1.69 (1.31, 2.18) Oral typical: 1.65 (1.32, 2.08) Quetiapine: 2.15 (1.71, 2.69) Risperidone: 1.30 (1.09, 1.54)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Haro, 2006 SOHO (secondary publication) 3-year remission/relapse outcomes Europe	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Haro, 2005 Europe SOHO (primary publication)	Prospectively collected, multicenter study data	Prospective	6 mo (interim analysis of planned 3-yr term)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Haro, 2005 Europe SOHO (primary publication)	NR	Olanzapine 12.1 mg/day (SD 5.9) Risperidone 4.9 mg/day (SD 2.8) Quetiapine 391 mg/day (SD 216) Clozapine 238 mg/day (SD 140)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Haro, 2005 Europe SOHO (primary publication)	Schizophrenia	Mean age 40 yrs 59.4% male Ethnicity NR	NR/NR/10972	1944/NR/9028 (at 6 months)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Haro, 2005 Europe SOHO (primary publication)	Outcomes at 6 months- EQ-5D VAS rating (mean): O 63.2 (SD 19.5) R 61.2 (SD 18.8); OR -2.3 (-3.4 to -1.2) vs olanzapine; p<0.0001 Q 59.9 (SD 19.9); OR -3.0 (-4.5 to -1.4) vs olanzapine; p<0.0001 C 61.0 (SD 20.3); OR 0.5 (-1.7 to 2.6) vs olanzapine Socially active: O 3990/4716 (84.6%) R 1410/1711 (82.4%); OR 1.27 (1.05 to 1.54) vs olanzapine; p<0.05 Q 544/690 (78.9%); OR 1.67 (1.29 to 2.16) vs olanzapine; p<0.001 C 246/301 (81.6%); OR 1.25 (0.87 to 1.80) vs olanzapine Relationship with spouse or partner: O 1467/4716 (31.1%) R 532/1711 (31.1%); OR 1.06 (0.81 to 1.39) vs olanzapine Q 206/690 (29.9%); OR 1.06 (0.72 to 1.57) vs olanzapine C 61/301 (20.3%); OR 1.23 (0.72 to 2.09) vs olanzapine Paid employment: O 1080/4716 (22.9%) R 370/1711 (21.6); OR 1.15 (0.88 to 1.51) vs olanzapine Q 206/690 (29.9%); OR 1.21 (0.81 to 1.81) vs olanzapine C 61/301 (20.3%); OR 1.66 (0.99 to 2.78) vs olanzapine Suicide attempt since baseline visit: O 75/4716 (1.6%) R 41/1711 (2.4%); OR 0.77 (0.47 to 1.25) vs olanzapine Q 10/690 (1.4%); OR 1.17 (0.52 to 2.66) vs olanzapine C 4/301 (1.4%); OR 0.92 (0.32 to 2.66) vs olanzapine

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Haro, 2005 Europe SOHO (primary publication)	NR	Only data abstracted for olanzapine, risperidone, quetiapine, clozapine arms

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Haro, 2009 SOHO (secondary publication) 36-month data from treatment discontinuation	Same as Haro 2005	Same as Haro 2005	36 months analysis
Alonso 2009 SOHO(secondary publication)HRQOL data			
Novick 2009 SOHO (secondary publication) Recovery data in the outpatient setting			
Novick 2009 SOHO (Tolerability of outpatient antipsychotic treatment.."			
Usall 2007 SOHO			

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Haro, 2009 SOHO (secondary publication) 36-month data from treatment discontinuation Alonso 2009 SOHO(secondary publication)HRQOL data Novick 2009 SOHO (secondary publication) Recovery data in the outpatient setting Novick 2009 SOHO (Tolerability of outpatient antipsychotic treatment.." Usall 2007 SOHO	NR	Mean endpoint doses olanzapine: 11.8 mg/day risperidone:4.5 mg/day quetiapine: 320mg/day

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Haro, 2009 SOHO (secondary publication) 36-month data from treatment discontinuation Alonso 2009 SOHO(secondary publication)HRQOL data Novick 2009 SOHO (secondary publication) Recovery data in the outpatient setting Novick 2009 SOHO (Tolerability of outpatient antipsychotic treatment.." Usall 2007 SOHO	Schizophrenia	Mean age: 34y 59% male Ethnicity: NR	NR/NR/1009	NR/236*/931 * lost to Follow-up before changing medication

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Haro, 2009 SOHO (secondary publication) 36-month data from treatment discontinuation	% of patients discontinuing treatment by 36 mo Olanzapine vs Risperidone vs typicals versus other atypicals 28.9% vs 36.2% vs 44.5% vs 34.7%
Alonso 2009 SOHO(secondary publication)HRQOL data	Cox proportional HR for discontinuation of treatment by 36 months- Higher than olanzapine for Risperidone and typical
Novick 2009 SOHO (secondary publication) Recovery data in the outpatient setting	Typicals: HR 1.76; 95% CI 1.11-2.78 Risperidone: HR 1.36 95% CI 1.02-1.82
Novick 2009 SOHO (Tolerability of outpatient antipsychotic treatment.."	HR for atypicals similar to olanzapine: Atypicals: HR 1.43 (95% CI, 0.85-2.40)
Usall 2007 SOHO	Patients with higher CGI-score at baseline had higher risk of discontinuing treatment at 36 months HR 1.18, 95% CI 1.06-1.30 EuroQOL-5D mean (SD) score at 36 mo: 0.80 (0.25) Factors associated with achieving long lasting symptomatic remission vs functional remission vs adequate QOL during 3 year follow-up OR with respect to Olanzapine Risperidone (OR): 0.785, p= 0.0062 vs 0.795 (p=0.795) vs 0.639 (p<0.0001) Quetiapine (OR)0.456 (p<0.0001) vs 0.760 (p=0.2121) vs 0.443 (p<0.0001) Clozapine (OR) 0.944 (p=7514) vs 0.555 (p0.0881) vs 1.101 (p=0.6098) Response overall CGI: OR for gender (female reference category) 95% CI, p-Value Olanzapine cohort 0.88 (0.78 to 1.00), p=0.040 Risperidone cohort 0.90 (0.74 to 1.10), p=0.2969 Clozapine 0.56 (0.34 to 0.93) p=0.252, p=0.0252 EQ-VAS change from baseline Difference in rating by gender (female reference category), 95% CI, p-value Olanzapine cohort: -1.52 (-2.53 to -0.50), p=0.0033 Risperidone cohort: 0.27 (-1.28 to 1.83), p=0.7300 Clozapine cohort: -2.03 (-6.06 to 2.00), p=0.3243

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Haro, 2009 SOHO (secondary publication) 36-month data from treatment discontinuation Alonso 2009 SOHO(secondary publication)HRQOL data Novick 2009 SOHO (secondary publication) Recovery data in the outpatient setting Novick 2009 SOHO (Tolerability of outpatient antipsychotic treatment.." Usall 2007 SOHO	% of patients with adverse events Olanzapine vs risperidone vs other typicals versus typicals EPS: 3.6% vs 17.1% vs 9.9% vs 13.7% TD: 0.4% vs 1.1% vs 1.7% vs 1.2% loss of libido/impotence: 25.5% vs 38.9% vs 37.9% vs 41.3% Prolactin-related: 3.8% vs 9.2% vs 10% vs 3.1% 7% weight gain: 30.8% vs 23.2% vs 22.7% vs 10.7% Tolerability (Novick 2009)Olanzapine vs risperidone vs quetiapine vs clozapine EPS % of patients with EPS at 36 mo 9.4% vs 15.6% vs 11.9% vs 12.9% OR (95% CI) in comparison to olanzapine Risperidone: 2.55 (2.16 to 3.02), Quetiapine 1.36 (1.02 to 1.81), Clozapine 1.19 (0.81 to 1.74) Tardive dyskinesia % of patients with tardive dyskinesia at 36 mo: 3.4% vs 4.8% vs 5.3% vs 7.1% OR (95 % CI) in comparison to olanzapine Risperidone: 2.47 (1.56 to 3.94), Quetiapine 1.77 (0.89 to 3.51) Clozapine 2.37 (0.96 to 5.85) Loss of libido/impotence % of patients with loss of libido/impotence at 36 mo 32.5% vs 36.5% vs 34.2% vs 40.9 OR (95% CI) in comparison to olanzapine Risperidone 1.38 (1.20 to 1.60), quetiapine 1.07 (0.86 to 1.33) vs 1.39 (1.04 to 1.86) mean (SD) Weight change from baseline to 36 mo: 4.2 (8.7) vs 2.7 (7.6) vs 1.7 (8.4) vs 2.6 (9.5) % of patients with >7% weight gain at 36 mo from baseline: 40.6% vs 33.7% vs 30.9% vs 29.5%	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Haro, 2008 10 European countries	Data from the SOHO (Schizophrenia Health Outcomes) study	Prospective observational study	3 year follow-up
Haukka 2008 Finland	National Hospital Discharge Register, Statistics Finland, and a nationwide prescription register.	Retrospective	January 1, 1997-December 31, 2003

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Haro, 2008 10 European countries	3 years	Olanzapine Is the reference medication Other medications include risperidoen, quetipine, amisulpride, clozapine, depot typicals
Haukka 2008 Finland	Not reported	clozapine olanzapine typical antipsychotics (haloperidol zuclopenthixol, other or mixed) antidepressants (fluoxetine, citalopram, paroxetine, sertraline, mianserin, other or mixed)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Haro, 2008 10 European countries	Patients at least 18 years of age with initiating or changing antipsychotic medication for the treatment of schizophrenia; presenting within the normal course of care in the outpatient setting or in the hospital when admission was planned for the initiation or change of antipsychotic medication and discharge planned within 2 weeks 5950 patients analyzed Mean duration of illness: 11.9 years 9% never treated for schizophrenia Concomitant medication: 19% on anticholinergics; 18% on antidepressants; 9% on mood stabilizers; 37% on anxiolytics CGI overall (SD): 4.4 (1.0)	Mean age: 40.3 years Male: 58% Ethnicity: NR	NR/NR/5950	NR/NR/5950
Haukka 2008 Finland	All individuals in Finland who (a) had been hospitalized with a diagnosis of attempted suicide, (b) had at least one hospitalization registered in the National Hospital Discharge Register with a schizophrenia diagnosis and (c) were at least 16 years of age when the index hospitalization began.	Median age 35.63 (males), 41.05 (females) 51% male Race not reported	NR NR 1,611	NR NR 1,611

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Haro, 2008 10 European countries	Remission was defined as a score of 3 (mild severity) or less on the CGI overall severity score, the CGI positive symptoms score, the CGI negative symptoms score and the CGI cognitive symptoms score that was maintained for a period of six months or more 2301 (38.7%) never achieved remission during the 3-year follow-up (prolonged course), 933 (15.7%) achieved remission but relapsed (remission and relapse) and 2716 (45.7%) achieved and maintained remission (persistent remission). "Patients prescribed risperidone, quetiapine or depot typicals at the baseline visit had a lower chance of achieving remission compared with those prescribed olanzapine" Relationship between independent variables (age of onset, years since onset, male, never treated before baseline, has a spouse/partner, paid employment, socially active, CGI overall, CGI positive, CGI negative, CGI cognitive, hostile behaviours, BMI, anxiolytics, and ood stabilizers) given in table. "Females, patients with better social functioning at baseline (living independently, in paid employment, socially active or having a spouse or partner) and with a shorter duration of illness had a more favourable course"
Haukka 2008 Finland	Propensity-score adjusted hazard ratios (95% CI) vs no antipsychotic use <u>Suicide attempts</u> Clozapine: 0.74 (0.35, 1.57) Olanzapine: 1.37 (0.87, 2.14) Haloperidol: 0.92 (0.46, 1.83) Perphenazine: 1.73 (0.89, 3.34) Other or mixed: 1.34 (1.10, 1.62) <u>Suicides</u> Clozapine: 0.67 (0.16, 2.85) Olanzapine: 0.40 (0.11, 1.44) Haloperidol: 1.03 (0.18, 5.98) Perphenazine: 0.27 (0.01, 4.73) Other or mixed: 0.62 (0.39, 0.98) <u>All-cause mortality</u> Clozapine: 0.57 (0.19, 1.71) Olanzapine: 0.31 (0.12, 0.79) Haloperidol: 0.50 (0.15, 1.65) Perphenazine: 0.20 (0.04, 1.06) Other or mixed: 0.54 (0.40, 0.74)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Haro, 2008 10 European countries	NR	
Haukka 2008 Finland	NA	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Hayhurst, 2002 UK	South Manchester University Hospitals NHS Trust	Retrospective cohort Controlled	NR
Hedenmalm, 2002 International	WHO database	Retrospective	Median treatment duration: R: 13 days, C: 52 days, O: 115 days
Hennessy, 2002 United States	3 US Medicaid programmes	Retrospective	NR
Herceg, 2008	Vrapce Psychiatric Hospital, Zagreb, Croatia	Retrospective	Jan 1, 2003-Dec 31, 2004

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Hayhurst, 2002 UK	2 years	Clozapine 425 mg/day other antipsychotics: not specified
Hedenmalm, 2002 International	NR	Risperidone Clozapine Olanzapine
Hennessy, 2002 United States	NR	Quarter 1, Quarter 2, Quarter 3, Quarter 4 clozapine: <243, 243-385, 386-543, >543 risperidone: <2.8, 2.8-5.0, 5.1-6.5, >6.5 haloperidol: <3.5, 3.5-7.5, 7.6-15.0, >15.0 thioridazine: <51, 51-102, 103-204, >204
Herceg, 2008	2 yrs	Risperidone vs olanzapine vs clozapine Newly diagnosed schizophrenia Mg/day, median, Interquartile (IQ) range 4 (4-6) vs 10 (10-15) vs 250 (200-300) Chronic schizophrenia Mg/Day, median, IQ range: 4(3-6) vs 15 (10.0-17.5) vs 200 (150-300)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Hayhurst, 2002 UK	Schizophrenia	Mean age: 42.5 y 65.1% male Ethnicity: NR	NR /NR /126	NR/ NR/ 126
Hedenmalm, 2002 International	Schizophrenia	NR NR NR	NR/NR/868	0/0/868
Hennessy, 2002 United States	Schizophrenia, control group of patients with psoriasis	71.5% over 34 yrs of age 54% Female Ethnicity NR	NR/NR/NR	NR/NR/NR
Herceg, 2008	Newly diagnosed schizophrenia and Chronic schizophrenia	risperidone vs olanzapine vs clozapine Newly diagnosed schizophrenia Age median, (IQ range): 24 (20-32) vs 27 (22-39) vs 33 (27-46) % male: 64.0% vs 44.0% vs 77.0% Chronic Schizophrenia Age, median (IQ range):38 (30-35) vs 36 (28.5-44.0) vs 40 (33.5-47.5) % male: 64.0% vs 53.0% vs 60.0%) Ethnicity: NR	NR/831/533	298/NR/533

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Hayhurst, 2002 UK	Reduction in mean number of admissions between 2y before clozapine and 2y after, clozapine vs. other: -0.54 vs + 0.25. p <0.01 Reduction in mean length (days) of stay between 2y before cloz. and 2 y after, clozapine vs. other: -33.37 vs -1.35d, p<0.05 % of clozapine users who came off clozapine in 2 years after starting: 44.4% mean reduction in bed-days over 2 yr follow-up period for cloz. users: -33 bed days
Hedenmalm, 2002 International	NR
Hennessy, 2002 United States	Adjusted rate ratios; 95% Cis Patients with glaucoma: cardiac arrest/ventricular arrhythmia; death: clozapine: 1.7 (1.0-2.9); 3.4 (2.1-5.5) haloperidol: 2.2 (1.7-3.0); 4.5 (3.6-5.7) risperidone: 3.1 (2.2-4.5); 5.8 (4.3-8.0) thioridazine: 2.2 (1.6-3.); 4.0 (3.1-5.2) Patients with psoriasis: cardiac arrest/ventricular arrhythmia; death: clozapine: 1.9 (1.0-3.7); 2.6 (1.5-4.5) haloperidol: 2.4 (1.5-3.9); 3.2 (2.2-4.8) risperidone: 3.2 (1.9-5.4); 4.1 (2.7-6.4) thioridazine: 2.4 (1.4-3.9); 2.9 (2.0-4.4)
Herceg, 2008	Newly diagnosed schizophrenia risperidone vs olanzapine vs clozapine % rehospitalized taking atypical antipsychotics:17.3% vs 19.2% vs 11.5, p=NS Time to first rehospitalization at 2 years: longest for olanzapine (difference with other groups, NS) chronic schizophrenia % rehospitalized taking atypical antipsychotics by the 2nd year follow-up: 13% vs 12% vs 14%, p=NS Time to first rehospitalization: longest for risperidone (Difference with other groups, NS)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Hayhurst, 2002 UK	NR	
Hedenmalm, 2002 International	74% of cases of discontinuation, glucose tolerance improved after discontinuation. After rechallenge (N=24) , following resulted in recurrence of glucose intolerance: clozapine: 18, olanzapine: 5, risperidone: 1	
Hennessy, 2002 United States	Those with treated schizophrenia has higher rates of cardiac arrest and ventricular arrhythmia over those non-treated: ratio: 1.7-3.2	
Herceg, 2008	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Ho, 1999 United States	Mental Health Clinical Research Center, University of Iowa	Retrospective	4 weeks
Hodgson, 2005 England	Case Notes: 26 consultant psychiatrists	Retrospective	1994 to 2001

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Ho, 1999 United States	6 months	Risperidone 6.0 mg/day (N=21) Olanzapine 13.7 mg/day (N=21)
Hodgson, 2005 England	NR	Clozapine=332.3mg/day Olanzapine=12.1mg/day Risperidone=4.7mg/day

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Ho, 1999 United States	Schizophrenia	Mean age: 31.5 years 76.2% male Ethnicity NR	NR/NR/42	NR/NR/26
Hodgson, 2005 England	Schizophrenia or schizoaffective disorder	Clozapine/Olanzapine/Risperidone Mean age (years)=37.3/41.8/39.4 % male=82/60/65	550/261/253	NR/NR/253

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Ho, 1999 United States	olanzapine vs risperidone, change from baseline, p value At discharge Symptom score: negative symptom dimension: -2.8(0.76)* vs -1.8(0.61)*, p=0.49 psychotic symptom dimension: -1.3(0.55)* vs -1.9(0.53)*, p=0.82 disorganized symptom dimension: -1.8(0.68)* vs -2.1(0.77)*, p=0.68 Total SANS/SAPS: -5.8(1.58)* vs -5.9(1.46)*, p=0.69 Total BPRS: -9.0(2.91)* vs -6.5(2.47)*, p=0.14 GAS score: 8.9(2.18)* vs 6.2(1.4)*, p=0.09 (*p<0.05 vs baseline, within group comparison) At follow-up Symptom score: negative symptom dimension: -1.5(0.94) vs -1.5(1.18), p=0.84 psychotic symptom dimension: -1.4(0.5)* vs -3.9(0.64)*, p=0.03 disorganized symptom dimension: -0.8(0.7) vs -3.2(1.1)*, p=0.36 Total SANS/SAPS: -3.7(1.23)* vs -8.6(2.39)*, p=0.3 GAS score: 8.8(4.01)* vs 13.9(2.43)*, p=0.52 Quality of life scores: occupational impairment: -0.5(0.43) vs 0.5(0.27), p=0.06 financial dependence: 0.7(0.27) vs 0.7(0.26), p=0.49 impairment in performance of household duties:-0.7(0.24)* vs -0.6(0.4), p=0.91 relationship impairment with family member: -0.01(0.27) vs -0.4(0.2), p=0.27 relationship impairment with friends: -0.4(0.29) vs -0.2(0.25), p=0.37 enjoyment of recreational activities: -0.8(0.36) vs -0.3(0.38), p=0.77 satisfaction: -0.5(0.22) vs -0.8(0.30), p=0.67 overall psychosocial functioning:-0.7(0.31) vs -1.15(0.22)*, p=0.24 (*p<0.05 vs baseline, within group comparison)
Hodgson, 2005 England	Patients treated with risperidone and clozapine were 1.3 and 0.56 times, respectively, more likely to discontinue compared to olanzapine Median time to discontinuation Risperidone=274 days Olanzapine=522 days Clozapine=6 years

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Ho, 1999 United States	EPS at discharge: SAS: 0(0.19), 0.4(0.56), p=0.31 BAS: -0.1(0.15) vs 0.6(0.20)*, p=0.001 (*p<0.05 vs baseline, within group comparison)	
Hodgson, 2005 England	One serious adverse event was reported: intussusception in a patient taking clozapine. Side effects were not a common primary reason for medication discontinuation and therefore were not reported by the authors.	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Hrdlicka, 2009	patients receiving routine clinical care at the department of child psychiatry	Retrospective	1997-2007
Jerrell, 2007 United States	Medical and pharmacy claims information	Retrospective	July 1, 2002 to June 30, 2004
Joyce, 2005 United States	Medical and pharmaceutical claims from the PharMetrics Patient-Centric Database	Retrospective	March 1, 2001 and August 31, 2003
Kane, 1993 United States	NR	Prospective	≥ 1 year

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Hrdlicka, 2009	6 weeks	Risperidone vs olanzapine vs ziprasidone vs clozapine Mean dose (SD) at week 6: 2.7 mg(1.3) vs 15.0mg (6.1) vs 80.0 mg(0.0) vs 247.5 mg(118.0)
Jerrell, 2007 United States	NR	Atypical antipsychotics: Aripiprazole Ziprasidone Quetiapine Risperidone Olanzapine Clozapine Typical antipsychotics: Haloperidol Fluphenazine
Joyce, 2005 United States	≥12 months	Risperidone: between 0.5mg and 8mg daily Olanzapine: between 2.5mg and 40mg daily Quetiapine: between 100mg and 800mg daily Ziprasidone: between 40mg and 160mg daily
Kane, 1993 United States	NR	Clozapine CAPD

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Hrdlicka, 2009	Schizophrenia, schizoaffective disorder and other schizophrenic disorders	Mean age, yrs (SD)15.8 (1.6) range (10.5-18.8) yrs % male: 47.7%	NR/109/109	52/NR/109
Jerrell, 2007 United States	Primary or secondary diagnosis of schizophrenia	51% of sample was ≥40 years of age 51% male 62% African American	NR/NR/2231	NR/NR/2231
Joyce, 2005 United States	Schizophrenia or Schizoaffective disorders	Ziprasidone/Risperidone/ Olanzapine Mean age (years): 40.1/43.4/45.3 % male: 36.9/42/44.9	NR/NR/1810	NR/NR/1810
Kane, 1993 United States	Schizophrenia/schizoaffective	Mean age=26.8 62.8% male Race NR	NR NR 437 (Clozapine=28, CAPD=409)	NR NR 437

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Hrdlicka, 2009	Risperidone vs olanzapine vs clozapine mean change in weight between baseline and week 6 (Kg): +3.6 (2.6) vs +4.4 (2.5) vs + 2.1 (4.0), p=0.286
Jerrell, 2007 United States	Health Outcomes For cerebrovascular conditions, there were no significant differences between groups For heart disease conditions, aripiprazole had a lower estimate for myocardial infarctions and ischemic heart disease compared to both typical antipsychotics (P=0.006), risperidone had a lower incidence rate for arrhythmias compared to both typical antipsychotics (P=0.007). The incidence rate for cardiomyopathy was significantly lower for aripiprazole than for both typical antipsychotics (P=0.02). The incidence of being diagnosed with incident hypertension was significantly higher for those taking ziprasidone compared to both typical antipsychotics (P=0.01)
Joyce, 2005 United States	Compliance and Persistence Compliance was significantly higher among those prescribed ziprasidone compared with the other treatment groups (P<0.01) Persistence in the first year was 30 days longer among those prescribed ziprasidone compared with the other treatment groups, though not significant (persistence in days: ziprasidone=228; risperidone=193; and olanzapine=201) Health Care Costs Ziprasidone treatment group had the highest total annual cost compared to the other two treatment groups. Though change in cost from pre- to post index periods was not significantly different among the treatment groups. Psychiatric-related costs decreased significantly more for the ziprasidone treatment group than the other two groups (risperidone, P=0.0116 and olanzapine, P=0.0021)
Kane, 1993 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Hrdlicka, 2009	NR	Weight gain data from ziprasidone not available at week 6 for statistical analysis because of early discharges and drop outs
Jerrell, 2007 United States	See outcomes column	
Joyce, 2005 United States	NR	
Kane, 1993 United States	Tardive dyskinesia Clozapine=2 cases CAPD=NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Kasper, 2001 9 countries in Europe and Australasia	Riverview Hospital , British Columbia	Retrospective	4 months
Karagianis, 2009 HOCCC study	9 Canadian provinces	Prospective	NR
Kim 2008 Korea	Comprehensive medical histories were collected from all available sources including patients, informants, and hospital medical records	Prospective	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Kasper, 2001 9 countries in Europe and Australasia	NR	Risperidone (N=30) : 4.89 mg/day vs. olanzapine (N=30): 17.19 mg/day
Karagianis, 2009 HOCCC study	1 year	Mean doses(SD) at 12 mo (mg/day) Olanzapine: 12.8 (8.2) Risperidone: 2.9 (1.7) Quetiapine:375.6 (SD 293.6) Clozapine: 332.8 (172.9)
Kim 2008 Korea	2 years	Mean modal dose (mg/day) Clozapine: 423.6±107.4 Risperidone: 7.6±2.9

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Kasper, 2001 9 countries in Europe and Australasia	Aged 18-60, schizophrenia-types: paranoid, schizoaffective--disorder, Bipolar affective disorder, undifferentiated	Mean Age: 35.7 years Male: 62% Ethnicity: NR	NR/NR/60	NR/NR/37
Karagianis, 2009 HOCCC study	schizophrenia or other related disorders	Olanzapine vs risperidone vs quetiapine vs clozapine Age (yrs), mean (SD) 43.4(11.6) vs 43.7 (11.5) vs 41.9 (11.1) vs 43.1 (12.4) % female: 48% vs 48.4% vs 45.8% vs 14.3% % Caucasian: 88.1% vs 84.7% vs 86.1% vs 94.7%	NR/NR/929	266/NR/796
Kim 2008 Korea	Schizophrenia and comorbid alcohol use disorders (AUD) Exclusion criteria: subjects with substance abuse other than alcohol, those with significant physical problems or organic mental disorders, and those with mental retardation	Clozapine/Risperidone Age (y): 39.5±9.4/38.7±10.5 Gender (% male): 100/100 Ethnicity: NR	NR 67 67	6 NR 61 (25 clozapine, 36 risperidone)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Kasper, 2001 9 countries in Europe and Australasia	Percentage of Patients Discharged on Original Therapy: R: 40% vs O: 13.3%; P<0.05 Treatment success: R: 40% vs O: 27%; P<0.01 Switched due to lack of efficacy: R: 37% vs O: 57%; P=NS Switched due to side effects: R: 10% vs O: 63%; P<0.05
Karagianis, 2009 HOCCC study	Olanzapine vs risperidone vs quetiapine v clozapine Proportion of treatment completers: 67.4% vs 62% vs 63.7% vs 55.6%, p=0.15
Kim 2008 Korea	Clozapine/Risperidone Community survival (%): 52/25 Mean survival (d): 526.5 (95% CI 435.0-498.6)/420.4 (95% CI 342.2-498.6) The survival curve for the clozapine group was significantly different from that of the risperidone group (log-rank test, *df*=1, P= .045)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Kasper, 2001 9 countries in Europe and Australasia	Treatment-emergent side effects: Total # of patients with side effects: R: 43.3% vs O: 40% EPS symptoms: 6/30 (20%) Akathisia: R: 5 vs O: 1 Stiffness: R: 2 vs O: 0 Tremor: R: 2 vs O: 1 Parkinsonism: R: 1 vs O: 0 Agitation: R: 1 vs O: 5 Increased prolactin level: R: 0 vs O: 1 Blurred vision: R: 0 vs O: 1 Increased salivation: R: 0 vs O: 1 Anxiety: R: 1 vs O: 0 Sedation: R: 5 vs O: 3 Hypotension: R: 2 vs O: 0 Dizziness: R: 1 vs O: 1 Weight Gain: R: 1 vs O: 1 Difficulty swallowing: O:1 vs R: 0 Sexual dysfunction: O: 1 vs O: 0	
Karagianis, 2009 HOCCC study	Olanzapine vs risperidone vs quetiapine v clozapine % of serious adverse events: 11.7% vs 8.9% vs 15.7% vs 21% 5 deaths in olanzapine group vs 1 from the other SGA group. Olanzapine vs risperidone vs quetiapine LS mean changes from baseline BMI were 0.7 (95% CI 0.1 to 1.2), 0.6 (95% CI -0.3 to 1.5) and -1.2 (95% CI -2.3 to -0.13). Olanzapine and risperidone groups had significantly higher increases in BMI(LS mean treatment effect 1.91 (95% CI: 0.41 to 3.42) and 1.86 (95% CI 0.13 to 3.58) respectively compared to quetiapine LS mean weight change from baseline(Kg): 2.0 (95% CI 0.4 to 3.6) vs 1.2 (95% CI -1.3 to 3.8) and -2.8 (95% CI -6.1 to 0.4). Olanzapine and risperidone significantly ore likely to gain weight compared to quetiapine (LS mean difference 4.8 and 4.0 respectively)	
Kim 2008 Korea	NR	Study subjects were 100% male

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Kilzieh 2008 United States	Electronic medical records database transformed into a data "warehouse" for data extraction	Retrospective	January 1999 through December 2000
Koller, 2003 United States	Food and Drug Administration Med Watch	Retrospective	9 years
Koro, 2002 UK	England and Wales-based General Practice Database, Bristol-Myers Squibb, MEDTAP	Retrospective	30 months
Koro, 2002b UK	United Kingdom based General Practice Research Database	Retrospective	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Kilzieh 2008 United States	NR	NR
Koller, 2003 United States	NR	Risperidone, haloperidol
Koro, 2002 UK	NR	Olanzapine: dose range NR Risperidone: dose range NR Conventional antipsychotics
Koro, 2002b UK	NR	Olanzapine: dose range NR Risperidone: dose range NR Conventional antipsychotics

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Kilzieh 2008 United States	Schizophrenia or schizoaffective disorder	Mean Age (y): 48.4±11.6 % Male: 91 Ethnicity: NR	NR NR 495 (221 Olanzapine, 274 Risperidone)	NR NR 495
Koller, 2003 United States	Patients prescribed study drugs	Mean age: 39.8 years 80% male Ethnicity NR	NR/NR/NR	NR/NR/NR
Koro, 2002 UK	Schizophrenia	Mean age: 51 years 60% Male	3.5 million /18,309/8866	0/0/8866
Koro, 2002b UK	Patients with prescriptions for both schizophrenia and diabetes	Mean age: 51 years 62.5% Female	3.5 million/3.5 million/19,637	0/0/19,637

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Kilzieh 2008 United States	Discontinuation rates: Index medication trials: 73% Olanzapine: 70% Risperidone: 76% (P=0.12) Higher discontinuation rate of risperidone: hazards ratio = 1.23; 95% CI 0.99-1.5 Median time (d) to discontinuation: 120 (95% CI 105-135) Median time (d) to discontinuation (olanzapine): 150 (95% CI 120-180) Median time (d) to discontinuation (risperidone): 90 (95% CI 71-109) olanzapine compared to risperidone, P=0.04 Self-discontinuation was the main method of discontinuation occurring in 48% of index trials, with no significant difference between olanzapine (50%) and risperidone (46%) (OR 0.86, 95% CI 0.60-1.23) Switching between 2 agents as a form of discontinuation: 25% of index trials More switching in risperidone (30%) than olanzapine (20%) (P=0.01; OR 1.72, 95% CI 1.13-2.61) Of patients who switched medication, 44% did so in the first month of trial. Observed more in risperidone (50%) than olanzapine (32%) (P=0.05)
Koller, 2003 United States	Risperidone-associated hyperglycemia: N=131 Combined risperidone-haloperidol associated hyperglycemia: N=7 Haloperidol-associated hyperglycemia: N=13 Reports of acidosis with absence of hyperglycemia: N=11
Koro, 2002 UK	NR
Koro, 2002b UK	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Kilzieh 2008 United States	NR	
Koller, 2003 United States	# Patients with serious adverse events: Acidosis-ketosis: 26 NMS-Like Symptoms: 12 Pancreatitis: 4 Death: 4	
Koro, 2002 UK	Odd of developing hyperlipidemia: compared with no antipsychotic exposure: olanzapine: (OR, 4.65; 95% CI, 2.44-8.85); P<.001 vs risperidone: (OR, 1.12; 95% CI, 0.60-2.11); P=.72 compared with use of conventional antipsychotics: olanzapine: (OR, 3.36; 95% CI, 1.77-6.39); P<.001 vs risperidone: (OR, 0.81; 95% CI, 0.44-1.52); P=.52	
Koro, 2002b UK	Odds ratio of risk of developing diabetes: Olanzapine vs non-treated 5.8; 95%CI: 2.0-16.7 Olanzapine vs typical APs: 4.2; 95%CI: 1.5-12.2 Risperidone vs non-treated : 2.2; 95%CI: 0.9-5.2 Risperidone vs typical APs: 1.6; 95%CI: 0.7-3.8	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Kraus, 1999 Germany	Max Planck Institute of Psychiatry	Retrospective	4 weeks
Kurz, 1995 Austria	Single center Active control	First-time clozapine users	Mean weeks: clozapine=23.2, haloperidol=5.2 23.2 weeks
Lambert, 2005 Australia	Medical record review	Retrospective	1998 to 2000

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Kraus, 1999 Germany	1 week	Clozapine: 170 mg/day Olanzapine: 13 mg/day Haloperidol: 5 mg/day
Kurz, 1995 Austria	Clozapine 193.7 mg Haloperidol 12.8 mg	Anticholinergics Beta blockers
Lambert, 2005 Australia	18 months	Risperidone: 2.7mg/day (non-affective psychosis) and 2.5mg/day (affective psychosis) Olanzapine: 10.3mg/day (non-affective psychosis) and 9.8mg/day (affective psychosis)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Kraus, 1999 Germany	Schizophrenia	Mean age: 37 years 43% Female	NR/NR/NR	NR/NR/44
Kurz, 1995 Austria	Tardive dyskinesia	Mean age=30.3 63.6% male Race NR	NR NR 151	NR NR Unclear
Lambert, 2005 Australia	Experiencing an episode of psychosis, non-affective psychosis, or affective psychosis	Mean age (years): 21.7 66% male	NR/NR/367	NR/NR/367

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Kraus, 1999 Germany	Mean scores at endpoint; p value from baseline clozapine: weight: 71.0 kg; P=0.001 leptin: 10.7 ng/ml; P=0.004 olanzapine: weight: 70.6 kg; P<0.001 leptin: 10.1 ng/ml; P=0.006 haloperidol: weight: 64.2 kg; P=0.94 leptin: 7.0 ng/ml; P=0.54 no treatment: weight: 69.1 kg; P=0.63 leptin: 7.3 kg; P=0.86
Kurz, 1995 Austria	NR
Lambert, 2005 Australia	Treatment variables Within affective group, those taking olanzapine had a significantly longer duration of treatment than those taking risperidone (p=0.02) Outcome measures (non-affective psychosis) No significant differences were noticed between groups on the CGI-S, GAF, and SOFAS 112 people (56.6%) in the risperidone group and 28 people (58.3%) in the olanzapine group reached full remission of positive symptoms Outcome measures (affective psychosis) There was a significantly better response to olanzapine compared to risperidone measured by the CGI-S score at endpoint (p=0.002), however scores on the CGI-BP, GAF, and SOFAS were not significantly different

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Kraus, 1999 Germany	NR	
Kurz, 1995 Austria	Signs of TD: clozapine=5 cases (all had already shown symptoms at baseline); Haloperidol=0	
Lambert, 2005 Australia	Extrapyramidal side effects overall (p<0.001), especially parkinsonism (p<0.001) and akathisia (p=0.015) occurred more often in the risperidone group. More patients on risperidone experienced prolactin elevation (p=0.014), while weight gain was more prevalent with olanzapine users (p<0.001)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Lambert, 2005 SOHO (secondary publication) 6-month tolerability results Europe (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK)	Same as Haro 2005	Same as Haro 2005	Initial recruitment period of 9/1/00-12/31/01
Lambert, 2006 United States	Veterans Health Administration of the Department of Veterans Affairs (VA)	Retrospective	October 1, 1996 to September 30, 2001

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Lambert, 2005 SOHO (secondary publication) 6-month tolerability results Europe (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK)	6 months	Same as Haro 2005
Lambert, 2006 United States	NR	Olanzapine Risperidone Quetiapine Haloperidol

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Lambert, 2005 SOHO (secondary publication) 6-month tolerability results Europe (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK)	Subset of patients who were only receiving one antipsychotic after the baseline visit	Mean age=40 56.6% male Ethnicity NR	10,972/8400/7436	NR/NR/7436
Lambert, 2006 United States	Schizophrenia	Olanzapine/Risperidone/ Quetiapine/Haloperidol Mean age (years): 50.3/51.1/50.6/52 % male: 94.1/93.2/91.7/95.1 % African American: 28.8/30.8/21.2/39.4 % Hispanic: 6.8/4.8/4.1/5.4	NR/NR/15767	NR/NR/15767

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Lambert, 2005 SOHO (secondary publication) 6-month tolerability results Europe (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK)	NR
Lambert, 2006 United States	There were no significant differences between groups in regards to increased risk of developing diabetes. When analyses were reproduced, including those excluded previously due to having been exposed to antipsychotic agents during the prior 12-week period, there was an increased relative risk of developing diabetes for all second-generation antipsychotics except for quetiapine. In this analysis, the relative risk associated with olanzapine was significantly greater than that associated with risperidone (P=0.02).

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Lambert, 2005 SOHO (secondary publication) 6-month tolerability results Europe (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK)	Mean weight change (kg)/adjusted difference compared to olanzapine (95% CI) Olanzapine: 2.4 Risperidone: 1.4/-1.0 (-1.3, -0.7) Quetiapine: 0.6/-1.2 (-1.6, -0.7) Amisulpride: 1.4/-0.7 (-1.4, 0.0) Clozapine: 2.3/0.1 (-0.6, 0.7)) Oral typical: 1.1/-1.3 (-1.8, -0.8) Depot typical: 1.1/-0.9 (-1.5, -0.3) Mean BMI change (kg/m^2)/adjusted difference compared to olanzapine (95% CI) Olanzapine: 0.9 Risperidone: 0.5/-0.4 (-0.5, -0.3) Quetiapine: 0.2/-0.4 (-0.6, -0.2) Amisulpride: 0.5/-0.2 (-0.5/0.0) Clozapine: 0.8/0.0 (-0.3, 0.2) Oral typical: 0.4/-0.5 (-0.7, -0.3) Depot typical: 0.4/-0.4 (-0.6, -0.1)	
Lambert, 2006 United States	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Lambert, 2005 United States	California Medicaid	Retrospective	July 1, 1997 to December 31, 2000
Lee, 2006 IC-SOHO sub-study in Asian country participants 12-month outcomes Korea, Taiwan and Malaysia	Same as Dossenbach 2004	Same as Dossenbach 2004	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Lambert, 2005 United States	NA	More than 12 weeks
Lee, 2006 IC-SOHO sub-study in Asian country participants 12-month outcomes Korea, Taiwan and Malaysia	12 months	Same as Dossenbach 2004

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Lambert, 2005 United States	Schizophrenia	NR	129341/34337/12637	NR/NR/12637
Lee, 2006 IC-SOHO sub-study in Asian country participants 12-month outcomes Korea, Taiwan and Malaysia	IC-SOHO patients from participating Asian countries	Mean age=34.7 years 50% male 100% Asian	1256/NR/898	100 (11%)/0 lost to fu/analyzed unclear

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Lambert, 2005 United States	NR
Lee, 2006 IC-SOHO sub-study in Asian country participants 12-month outcomes Korea, Taiwan and Malaysia	Response rates (overall CGI-S score improved by ≥ 2 points from a baseline score of ≥ 4, or improved by ≥ 1 point from a baseline score of 3): Olanzapine=76.3% Risperidone=72.7% Typical antipsychotics=50% OR of response for typical agent vs olanzapine: 0.38 (p=0.010) (CI NR)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Lambert, 2005 United States	Odds ratios for conditional logistic regression model predicting development of hyperlipidemia 12-week exposure: n, OR, p(95% CI) clozapine: 879, 1.16, 0.07(0.99-1.37) olanzapine: 3322, 1.20, 0.00 (1.08-1.33) quetiapine: 322, 1.01, 0.92(0.78-1.32) risperidone: 2612, 1.00, 0.98(0.90-1.12) 24-week exposure: n, OR, p(95% CI) clozapine: 766, 1.22, 0.03(1.03-1.45) olanzapine: 2935, 1.24, <0.0001 (1.12-1.38) quetiapine: 243, 0.83, 0.25(0.61-1.13) risperidone: 2365, 1.01, 0.91(0.90-1.13) 52-week exposure: n, OR, p(95% CI) clozapine: 603, 1.20, 0.06(0.99-1.46) olanzapine: 2036, 1.17, 0.01 (1.04-1.32) quetiapine: 140, 0.80, 0.27(0.53-1.20) risperidone: 1819, 0.94, 0.34(0.83-1.27)	
Lee, 2006 IC-SOHO sub-study in Asian country participants 12-month outcomes Korea, Taiwan and Malaysia	<u>Tardive dyskinesia</u> % patients: olanzapine=7.9% risperidone=13.3% typicals=13% OR (95% CI): risperidone vs olanzapine=1.04(0.34-3.14) typicals vs olanzapine=4.23(1.02, 17.47) typicals vs risperidone=4.08(0.83, 19.94) <u>Weight increase of ≥ 7%</u> % patients: olanzapine=51.4% risperidone=29.8% typicals=20.5% OR (95% CI) risperidone vs olanzapine=0.38 (0.21, 0.68) typicals vs olanzapine=0.27 (0.12, 0.64) typicals vs risperidone=0.72 (0.29, 1.81)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Lee, 2002 United States	Database: Protocare Sciences' administrative claims and enrollment info	Retrospective	Index dates of patients occurred during a 27-month period (1997-1999). Mean duration of therapy: AAPs: 126.1 days Typical APs: 108.34 days
Leon, 1979 Colombia	Hospital Psiquiatrico, Colombia	Retrospective	6 weeks
Leslie, 2004 United States	Department of Veteran Affairs	Retrospective	3 months
Lin, 2006 Taiwan	Chart reviews	Retrospective	7/1/01-6/30/02

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Lee, 2002 United States	Patients were observed 365 days after their index dates.	Clozapine Olanzapine Quetiapine Risperidone Typical APs Mean doses NR
Leon, 1979 Colombia	3-4 years	NR
Leslie, 2004 United States	NR	Clozapine, olanzapine, quetiapine, risperidone: mean doses NR
Lin, 2006 Taiwan	2 years	Clozapine, risperidone, typical antipsychotics

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Lee, 2002 United States	Patients aged 18-65 selected by first (index) AP/AAP prescription between Sept 1997-Dec 1999; excluded those who filed a claim for an AP/AAP within 180 days, or filled a Rx for a diabetes medication or had a DM diagnosis within 365 days before index date. Also excluded patients using concomitant AP meds on index date.	Mean age 44 41.4% male Ethnicity NR	NR 2315 2315 AAPs n=1334 Olanzapine n=513 Risperidone n=750 Clozapine n=5 Quetiapine n=66 Typical APs n=981	NR NR 2315 analyzed
Leon, 1979 Colombia	Schizophrenia	Mean age: 30.6 years 58% male Ethnicity NR	NR/NR/50	NR/NR/39
Leslie, 2004 United States	Schizophrenia	NR/NR/NR	56,849/56,849/56,849	0/0/56,849
Lin, 2006 Taiwan	Schizophrenia	82% male Mean age=39.2 years 100% Taiwanese	NR/NR/382	83 (22%)/NR/382

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Lee, 2002 United States	NR
Leon, 1979 Colombia	Mean number of required re-hospitalizations: clozapine: 1.89 vs chlorpromazine: 3.52; P<0.01 Average time spent in hospital: clozapine: 44.8 days vs chlorpromazine: 272.8 days; P<0.05 Average mean time for re-admission: clozapine: 260 days vs chlorpromazine: 229
Leslie, 2004 United States	NR
Lin, 2006 Taiwan	Typical antipsychotic vs clozapine vs risperidone: <u>360 days follow-up period</u> Mean time to rehospitalization (days): 244 vs 240 vs 262, p=NS Event rate: 49.6% vs 44.3% vs 43%, NS <u>720-day follow-up period</u> Mean time to rehospitalization (days): 378 vs 403, vs 426, NS Event rate: 57.7% vs 49.2% vs 53.1%, NS

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Lee, 2002 United States	Adjusted odds (95%CI) of diabetes onset within 1-year after index date: Atypicals vs typicals: 1.01 (0.61-1.67) Olanzapine vs typicals: 0.86 (0.43-1.73) Risperidone vs typicals: 1.07 (0.61-1.89) Olanzapine vs risperidone 0.79 (0.38-1.61)	
Leon, 1979 Colombia	NR	
Leslie, 2004 United States	7.3% diagnosed with diabetes will on treatment Highest risk: clozapine: 2.03%, quetiapine: 0.80%, olanzapine: 0.63%, risperidone: 0.05%	
Lin, 2006 Taiwan	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Liperoti 2009 USA	SAGE database containing MDS; data is from 1581 nursing homes in 5 US states	Retrospective	Jan 1998-Dec 2000
Lucey, 2003 Ireland	Irish Risperidone Olanzapine Drug Outcomes in Schizophrenia	Retrospective	Mean duration: 37.8-40.5 days
Madhusoodanan, 1999 United States	St. John's Episcopal Hospital	Retrospective	4 months

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Liperoti 2009 USA	6 months following first use of any antipsychotic.	Atypical antipsychotics (N=6524) Risperidone: n=4406 Olanzapine N=1563 Quetiapein N=497 Clozapine N=59 Conventional antipsychotics (N=3205), most frequently haloperidol (N=1413) and phenothiazines (N=546) Mean dose NR.
Lucey, 2003 Ireland	NR	risperidone: 4.2 mg/day olanzapine: 12.9 mg/day
Madhusoodanan, 1999 United States	NR	Mean daily doses: risperidone(N=114): 3mg olanzapine(N=37): 10mg

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Liperoti 2009 USA	Nursing home residents with dementia, aged 65+ who were new users of antipsychotics. Excluded comorbid schizophrenia.	Mean age: 84 72% male 90.7% White 8.4% Black	61,781 exposed 9,729 eligible (1st-time monotherapy users) All 9729 eligible were included.	No withdrawals. Loss to followup NR. 9729 analyzed.
Lucey, 2003 Ireland	Schizophrenia, schizoaffective disorder	Mean age: 37 years 55.5% Male Ethnicity NR	NR/396/394	0/0/396
Madhusoodanan, 1999 United States	schizophrenia, schizoaffective disorder, dementia, bipolar disorder, major depressive w/psychotic features, delusional disorder	Mean age: 71 years 60.5% Female Ethnicity NR	NR/NR/151	22%/NR/151

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Liperoti 2009 USA	NR
Lucey, 2003 Ireland	Hospital Stay: % discharged on or before day 120: R 95% vs O 94% (NS) Mean length of study duration: O 30 days vs R 26 day (p=0.27) Duration of hospital stay: O 40.5 vs R 37.8 (p=0.90) Distribution function curve of time to discharge: 'similar', p = 0.0.54
Madhusoodanan, 1999 United States	% of patients who responded to treatment: R: 78% vs O: 75% CGI scores: Very much/much improved: R: 78% vs O: 75% Minimally improved: R: 56% vs O: 24% No change: R: 20% vs O: 8%

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Liperoti 2009 USA	Risk of mortality is 26% greater with haloperidol vs atypical antipsychotics. Effect of conventional APs on increased mortality seen only in non-Alzheimer's dementia; absent among those with Alzheimer's dementia. Mortality during 6 months after index prescription, crude incidence per 100 person-years: Atypical antipsychotics: 40.0 Conventional antipsychotics: 54.3 HR for conventional vs atypical APs adjusted for age, race/ethnicity, gender, BMI, ADL score, Cognitive Performance Scale score, severity of behavioral symptoms, cardiovascular and cerebrovascular comorbidities, and use of concomitant medications (including cardiovascular drugs, aspriin/sntiplatelets/anticoagulants, benzodiazepines, and antidepressants: Residents with Alzheimer's Disease, HR = 1.02 (95%CI 0.75-1.39) Residents with other dementias (non-Alzheimer's), HR = 1.31 (95%CI 1.14,1.50) Haloperidol vs risperidone, adjusted HR: 1.31 (95%CI 1.13-1.53). Mortality was similar among AAPs.	
Lucey, 2003 Ireland	NR	
Madhusoodanan, 1999 United States	Adverse events reported: R: 20%; EPS, tremor, sedation, hypotension, diarrhea, tardive dyskinesia, chest pain, anxiety, restlessness, itching, insomnia and fall O: 16%; sedation, EPS, postural hypotension	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
McIntyre, 2003 Williams, 2006 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Naturalistic: 32 university and community sites across Canada	Prospective	June 1999 and November 2000
Medved , 2009 Croatia	cohort of patients admitted to the Department of Psychiatry, Zagreb University Hospital Centre	Prospective	2004 to 2007
Meyer, 2002 United States	Oregon State Hospital	Retrospective	July and August 1999

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
McIntyre, 2003 Williams, 2006 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Olanzapine=333 Quetiapine=324 Risperidone=280 (days)	Olanzapine 14.7 mg Quetiapine=324mg Risperidone=3.5 mg
Medved , 2009 Croatia	3 months	Orally administered olanzapine 5-20 mg/day or risperidone 2-5 mg/day for 3 months (±1 week) during 3-6 weeks of hospital treatment and followed by outpatient treatment. Mean olanzapine dose (SD): 11.51 (3.9) Mean Risperidone dose (SD): 3.16 (1.09)
Meyer, 2002 United States	1 year	risperidone (N=47): 4.5 mg/day olanzapine (N=47): 16.7 mg/day

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
McIntyre, 2003 Williams, 2006 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Consecutive outpatients with schizophrenia, schizophreniform disorder, schizoaffective disorder, or psychosis NOS	Mean age=36.8 67.9% male Race NR	NR NR 243 (Olanzapine=109, Quetiapine=23, Risperidone=111)	NR NR 243 analyzed
Medved , 2009 Croatia	Patients who were previously unmedicated (no antipsychotic medication) prior to admission and were diagnosed with DSM-IV schizophrenia spectrum disorders (DSM-IV criteria met for schizophrenia, schizoaffective disorder or delusional disorder, and no other neurological diseases, mental disorders, drug and alcohol abuse and eating disorders). Patients with menstrual cycle irregularities, pregnant, lactating or required treatment with medications other than diazepam and clonazepam for occasional insomnia were not included.	Mean age (SD): 31.07 (7.86) 100% female 100% Caucasian	NR/NR/94	0/0/94
Meyer, 2002 United States	Schizophrenia, schizoaffective disorder	Mean age:44.5 years 41% 87% Male Ethnicity NR	NR/396/394	Withdrawn=N/A (retrospective) Lost to follow-up=N/A (retrospective) Analyzed=94

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
McIntyre, 2003	Admission to hospital for any reason: n/N (%)
Williams, 2006 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Initial assessment to year 1; year 2 Clozapine: 9/59 (15.2%); 12/51 (23.5%) Olanzapine: 7/87 (8%); 9/70 (12.8%) Quetiapine: 5/20 (25%); 5/16 (31%) Risperidone: 10/97 (97%); 14/80 (17.5%)
Medved , 2009 Croatia	NR
Meyer, 2002 United States	Fasting triglyceride levels at one year: R: mean increase of 29.7 mg/dL vs O: 88.2 mg/dL Weight increases at one year: R: 11.7-13.9lb vs O: 15.0-26.0lb

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
McIntyre, 2003 Williams, 2006 Canada	Mean weight gain (kg) Olanzapine=3.72 Quetiapine=7.55 Risperidone=1.62	
Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	≥ 7% weight gain (% pts) Olanzapine=24.1% Quetiapine=55.6% Risperidone=23.7% Quetiapine vs risperidone=OR 3.62, 95% CI 1.02 to 12.83 ≥ 10% weight gain (% pts) Olanzapine=18.5% Quetiapine=38.9% Risperidone=13.2% Quetiapine vs risperidone=OR 3.91; 95% CI 1.02 to 15.08	
Medved , 2009 Croatia	Olanzapine: 10 (19%) drowsiness; 1 (2%) extrapyramidal syndrome (EPS); 1 (2%) edema Risperidone: 6 (16%) drowsiness; 2 (5) galactorhea; 1 (2.4%) EPS 27% patients with metabolic syndrome after 3-month compared to 15% of patients at baseline. Increase in BMI (SD) of 2.44 (3.01). "BMI was found to be a significant predictor of metabolic syndrome after second-gereration antipsychotics treatment"; *P*<0.001	
Meyer, 2002 United States	Triglycerides: O: + 104.8 mg/dL vs R: +31.7 mg/dL (P=.037) Cholesterol: O: +30.7 mg/dL vs R: +7.2 mg/dL (P=.004) Glucose: O: +10.8 mg/dL vs R: +0.74 mg/dL (P=.030)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Miller, 1998 United States	Innsbruck University Clinics, Austria	Retrospective	≥3 months
Modai, 2000 Israel	Database: Sha'as Menashe Mental Health Center (Israel)	Unclear	1/91 to 8/97
Mohamed, 2009 United States	Database: National administrative databases; and the Veterans Affairs Drug Benefit Management System files	Retrospective	2006
Moisan, 2005 Canada	Database from the Prescription Drug Insurance Plan administered by the Quebec Health Insurance Board	Retrospective	January 1, 1997-August 31, 1999

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Miller, 1998 United States	NR	clozapine: 425.6 mg/day risperidone: 4.7 mg/day conventional antipsychotics: 476.5 mg/day
Modai, 2000 Israel	NR	Clozapine Other psychiatric agents (non-clozapine treated)
Mohamed, 2009 United States	2 year follow-up	Long-acting injectable risperidone or oral antipsychotics
Moisan, 2005 Canada	NR	Olanzapine Risperidone

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Miller, 1998 United States	Schizophrenia, schizoaffective disorder, personality disorder, paranoid subtype	Mean age: 36.6 years 57.5% Male White: 71.7% Black: 2.6% Hispanic: 3.8% Asian: 1.9%	NR/NR/NR	0/0/106
Modai, 2000 Israel	Schizophrenia	NR NR NR	NR 5479 5479	NR NR 5479 (Clozapine=561 vs Non-clozapine=4918)
Mohamed, 2009 United States	All veterans seen at Veterans Affairs medical centers nationally who received a prescription for any new antipsychotic medication during fiscal year 2006 and had a diagnosis of schizophrenia. Prescriptions were considered new if there were no prescriptions for the drug during the last 6 months of fiscal year 2005.	32.4% at age 40-49 years 48.9% at age 50-64 years 8.6% at age >65 years 93.4% male 21.5% Black 5.1% Hispanic 1.1% Other 20% unknown race	11821/11821/11821	0/0/11821
Moisan, 2005 Canada	All drug beneficiaries who had received at least one prescription of an atypical antipsychotic drug during the time period and was under the age of 65.	% in each age group: 0-29 years=20.4 30-44 years=43.8 45-59 years=29.9 60-64 years=6.0 % male: 51.5	38043/19582/19582	NR/NR/19582

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Miller, 1998 United States	Simpson-Angus Scale scores: Akinesia>0: C: 17.1% vs R: 30.4% vs Conventionals: 38.1% Arm dropping>0: C: 12.2% vs R: 30.4% vs Conventionals: 35.4% Gait>0: C: 4.9% vs R: 21.7% vs Conventionals: 23.8% Salivation>0: C: 36.6% vs R: 8.7 vs Conventionals: 4.8% Tremor>0: C: 19.5 vs R: 21.7% vs Conventionals: 40.5%
Modai, 2000 Israel	NR
Mohamed, 2009 United States	Hazard ratio for discontinuing antipsychotics as compared to long acting injectiable risperidone: Aripiprazole: 2.76; *P*=0.0001 Clozapine: 0.37; *P*=0.0001 Conventional: 0.83; *P*=0.0003 Olanzapine: 0.83; *P*=0.0017 Quetiapine: 0.78; *P*=0.0001 Risperidone: 0.83; *P*=0.0002 Ziprasidone: 0.96; *P*=0.5516
Moisan, 2005 Canada	Those taking olanzapine were more likely to need to be started on a diabetic and/or lipids medication than those taking risperidone

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Miller, 1998 United States	Point prevalence of Akathisia: C: 7.3% vs R: 13% vs Conventionals: 23.8% Point prevalence of Rigidity: C: 4.9% vs R: 17.4% vs Conventionals: 35.7% Point prevalence of Cogwheeling: C: 2.4% vs R: 17.4% vs Conventionals: 26.2%	
Modai, 2000 Israel	Sudden death=6 (1.07%) vs 14 (0.28%); p<0.01 Disease-related death=2 (0.35%) vs 86 (1.75%); p<0.05 Total death=10 (1.78%) vs 105 (2.13%); NS Suicide 2 (0.35%) vs 5 (0.10%); NS	
Mohamed, 2009 United States	NR	
Moisan, 2005 Canada	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Montes, 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Multicenter Controlled	Subjects that required antipsychotic treatment for a first episode of schizophrenia, with an evolution of the illness of less than one year and who were not over the age of 40. Choice of new drug was made by the treating physician.	6 months
Mullins 2008 Maryland	All pharmacy and medical service encounter and fee-for-service claims from the Maryland Medicaid FFS and HealthChoice programs	Retrospective	January 1, 2001 to December 31, 2003
Novick, 2005 SOHO (secondary publication) Europe	Prospectively collected, multicenter study data	Prospective	6 mo (interim analysis of planned 3-yr term)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Montes, 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Olanzapine 13.5 mg Risperidone 5.4 mg Haloperidol 12.4 mg	High potency antipsychotics Low potency antipsychotics Benzodiazepines Anticholinergics Antidepressants Mood stabilizers
Mullins 2008 Maryland		NR
Novick, 2005 SOHO (secondary publication) Europe	NR	Olanzapine 11.8 mg/day (SD 5.7) Risperidone 4.9 mg/day (SD 2.7) Quetiapine 375 mg/day (SD 201) Clozapine 235 (SD 134)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Montes, 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Weight gain	Mean age=24.2 64.8% male Race NR	NR NR 182	45 (24.7%) withdrawn 24 (13.2%) lost to fu 182 analyzed
Mullins 2008 Maryland	Maryland Medicaid recipients aged 18-64 having a claim for schizophrenia any time during the three year study period for any of the 5 atypicals (aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone)	Aripiprazole/Olanzapine/Quetiapine/Risperidone/Ziprasidone Age Group (%) 18-39: 39.9/43.5/41.9/41.7/49.9 40-54: 48.4/44.5/47.1/46.5/42.1 55-64: 11.7/12.0/11.0/11.8/8.0 Gender (% male) 52.2/54.1/47.6/46.9/49.1 Ethnicity White: 53.6/39.1/47.5/38.5/48.7 Black: 46.4/60.9/52.5/61.5/51.3	NR NR 5898 (1705 olanzapine, 1580 risperidone, 1467 quetiapine, 700 ziprasidone, 466 aripiprazole)	NR NR 5898 (1705 olanzapine, 1580 risperidone, 1467 quetiapine, 700 ziprasidone, 466 aripiprazole)
Novick, 2005 SOHO (secondary publication) Europe	Schizophrenics receiving antipsychotic monotherapy	Mean age 39.6 yrs 57% male Ethnicity NR	10972/8057/6931 (olanzapine, risperidone, quetiapine and clozapine cohorts only)	765/NR/6931 (olanzapine, risperidone, quetiapine and clozapine cohorts only)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Montes, 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	NR
Mullins 2008 Maryland	Hazard ratios of discontinuation (95% CI), P value: Olanzapine: reference Aripiprazole: 1.047 (0.919-1.193), 0.4911 Quetiapine: 1.130 (1.039-1.230), 0.0044 Risperidone: 0.973 (0.897-1.055), 0.5014 Ziprasidone: 0.990 (0.891-1.100), 0.8514 Age: 0.997 (0.994-1.000), 0.0348 Black: 1.058 (0.994-1.127), 0.785 Male: 0.899 (0.845-0.957),0.0008 Psychiatric hospitalization: 1.276 (1.192-1.367), <0.0001 Concurrent medications: 0.225 (0.210-0.241), <0.0001 Adjusted medication continuation/discontinuation rates: Median time to discontinuation (d)/180-day continuation rate (%)/365-day continuation rate (%) Aripiprazole: 58/19.1/9.0 Olanzapine: 59/20.6/10.0 Quetiapine: 54/16.8/7.4 Risperidone: 61/21.5/10.7 Ziprasidone: 59/20.9/10.3
Novick, 2005 SOHO (secondary publication) Europe	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Montes, 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Weight gain (% patients) Olanzapine=15 (13.2%) Risperidone=1 (3.2%) Haloperidol= 0 p<0.05 for olanzapine > risperidone and haloperidol groups	First Episodes
Mullins 2008 Maryland	NR	
Novick, 2005 SOHO (secondary publication) Europe	Proportion of pts reporting weight gain: O 2993/4428 (67.6%) v R 946/1617 (58.5%) v Q 300/610 (49.2%) v C 157/276 (56.9%) Subgroup: concomitant medication use - proportion of pts reporting weight gain: O 1772/2546 (69.6%) v R 581/972 (59.8%) v Q 183/373 (49.1%) v C 118/183 (64.5%)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Ollendorf, 2004 United States	Database: PharMetrics Patient-Centric Database	Retrospective	1995-2001 Mean duration of therapy was 9 months in both typical AP and AAP groups; mean number of prescriptions was higher in AAP group: 8.5 vs 6.6, p<0.0001
Opolka, 2003 United States	Medical claims data from the Texas Medicaid Management Information System and pharmacy claims data from the Texas Vendor Drug Program paid prescription claims database	Retrospective	January 1, 1996 to August 31, 1999
Ostbye, 2004 United States	Database: AdvancePCS records on prescription drugs dispensed to beneficiaries (n=170030 from 50 states)	Retrospective	2000-2002

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Ollendorf, 2004 United States	Minimum of 3 months; mean 435 days	Olanzapine n=937 Risperidone n=690 Quetiapine n=164 Clozapine n=35 Mean dose NR
Opolka, 2003 United States	NR	Haloperidol Risperidone Olanzapine
Ostbye, 2004 United States	18 months	Primary exposure: subjects who filled prescriptions for any AAP at any time during the follow-up period. Primary control: subjects who filled prescriptions for typical AAPs during followup. Other control groups received antibiotics; antidepressants

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Ollendorf, 2004 United States	Patients with ≥1 medical claims with a diagnosis of schizophrenia, as well as ≥1 paid pharmacy claims for an AP medication during 1996-2001; the first observed antipsychotic pharmacy claim in this period was the index date. All medical and pharmacy claims were then compiled for these patients for the exposure period. Patients who used an AP or typical AP in the 6 months prior to the index date, or had evidence of DM within 12 months prior to the index date were excluded.	Mean age 39.1 48.2% male Ethnicity NR	18,134 2443 2443	NR NR 2443
Opolka, 2003 United States	Schizophrenia, schizoaffective disorder	Mean age: NR Gender: NR 45% White 39% African American	NR/NR/3583	NR/NR/3583
Ostbye, 2004 United States	Subjects for whom the first prescription for an exposure drug occurred after the 6-month lead-in period. The primary exposure group was subjects who filled prescriptions for an AAP in the followup period. The primary control group was subjects who filled prescriptions for typical APs in the followup period.	Mean age 41.9 38.1% male Ethnicity NR	NR NR 170,030	NR NR 170030

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Ollendorf, 2004 United States	NR
Opolka, 2003 United States	Adherence to index antipsychotic Risperidone users were 15% less adherent than olanzapine users (30 days less use/study period, P<0.001) Haloperidol users were 33% less adherent than olanzapine users (65 days less use/study period, P<0.001) and 21% less adherent than risperidone users (35 days less use/study period, P<0.001) African Americans were 12% less adherent than whites (24 days less use/study period, P<0.001) Mexican Americans were 13% less adherent than whites (25 days less use/study period, P=0.003) and 1% less adherent than African Americans (2 days less use/study period, P=0.838)
Ostbye, 2004 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Ollendorf, 2004 United States	Patients treated with AAPs had an increased risk of diabetes mellitus after 1 year, compared with typical APs: hazard ratio 1.17, 95% CI 1.06-1.30 No differences between olanzapine, risperidone, quetiapine, and clozapine were found on risk of diabetes.	This analysis controlled for total duration of therapy and number of prescriptions. Actual mean doses are not reported.
Opolka, 2003 United States	NR	
Ostbye, 2004 United States	Primary outcome was a new prescription filled for any antidiabetic drug during followup period, excluding those filled prior to the first prescription of an AP or AAP. Adjusted ORs (95% CI); AAPs: 1.70 (1.58-1.83) Typical APs: 2.08 (1.88-2.30) Antidepressants: 2.12 (1.96-2.30) Antibiotics: referent group In subjects that used only one drug class during study period: AAPs 0.86 (0.60-1.23) Typical APs: referent group Antidepressants 1.08 (0.81-1.45) Antibiotics 0.68 (0.50-0.92)	Exposure classification is binary (did or did not receive prescription for each drug or class); dose and duration of treatment are not controlled for

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Peacock, 1996 Denmark	Naturalistic: St. Hans Hospital; Copenhagen's Municipal Psychiatric Hospitals in Glostrup and Ballerup	Prospective	1 year
Pelagotti, 2004 Italy	Inpatients to a hospital Psychiatric Unit or as outpatients to a Psychiatric Ambulatory Clinic.	Retrospective	15 May 2002 to 20 August 2002

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Peacock, 1996 Denmark	NR	Clozapine CAPD
Pelagotti, 2004 Italy	Median 11.9 months	Olanzapine daily dose (mg) 13.3 (n=283) Risperidone daily dose (mg) 5.7 (n=170)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Peacock, 1996 Denmark	Schizophrenia	Mean age=41.5 69.5% male Race NR	NR NR 200	42(21%) withdrawn Lost to fu NR 158 analyzed (clozapine-=82, CAPD=76)
Pelagotti, 2004 Italy	Diagnosis of schizophrenia; ≥ 18 years; treatment with either olanzapine or risperidone at the date of enrollment; ‘‘Stable’’ therapy over the previous 4 months; Cumulative dose in this period of at least 80% of the respective defined daily doses (DDD values: olanzapine, 10 mg/day; risperidone, 5 mg/day).	Mean age 40 years 61.8% male Race NR	454/NR/144	NR/NR/144

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Peacock, 1996 Denmark	NR
Pelagotti, 2004 Italy	Dropout rate in the primary analysis (with a follow-up of 7 months: 4 switches from olanzapine to risperidone versus 11 switches from risperidone to olanzapine, P = 0.01) and in the secondary analysis (with a follow-up longer than 7 months: 9 switches from olanzapine versus risperidone and 17 switches from risperidone to olanzapine; P = 0.004).

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Peacock, 1996 Denmark	Clozapine versus control: Potentially new: Overall tardive dyskinesia (TD): relative advantage of clozapine=36% (95% confidence limits=21-50%; *P*<0.001) Oral TD (# cases): 9 vs 19; NS Extremity TD (# cases): 5 vs 22; *P*<0.001 TD 1-year follow-up Prior TD "disappeared" (# cases): 3 vs 1, *P-value* NR Prior TD "reappeared" (# cases): 2 vs 0, *P-value* NR New cases still present: clozapine=all 11, control=all but 1 Further potentially new cases: 0 vs 4 Parkinsonian signs at first examination: 33% vs 61%; relative advantage of clozapine=28% (95% CL 15-41%, *P*<0.001) Parkinsonian symptom severity (# patients with global score of ≥ 3): 8 vs 32, *P*<0.05 Parkinsonism source (# cases; relative advantage of clozapine, 95% CL): Rigidity: 0 vs 19; *19% (95% CL 11-27%,* P<*0.001)* Tremor: 3 vs 11; 8% (95% CL 1-15%, *P*=0.05) Psychic akathisia (% patients): 14% vs 40%; *P*<0.001 Motor akathisia (% patients): 7% vs 29%; *P*<0.001 Mild finger dystonia (# patients): 1 vs 10; *P*<0.05	
Pelagotti, 2004 Italy	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Peuskens 2009 Belgium	Participants were recruited from university hospitals, general and psychiatric hospitals and ambulatory practice	Prospective	2 years
Philippe, 2005 France	Principal public psychiatric care units in France	Prospective	1993 to 2002

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Peuskens 2009 Belgium	Haloperidol/Olanzapine/Risperidone Mean treatment duration (d) based on 294 patients: 476±248/545±232/513±257	Haloperidol/Olanzapine/Risperidone Mean dose (mg/d) based on 294 patients: 8.9±6.8/14±6/4.2±1.9
Philippe, 2005 France	Nine years	Conventional antipsychotics Risperidone Olanzapine Clozapine Amisulpride

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Peuskens 2009 Belgium	Adults diagnosed with schizophrenia or schizophreniform disorder and stabilized with haloperidol/haloperidol decanoate, olanzapine or risperidone monotherapy ≤ 1 month following discharge from full-time (maximum 6 month) hospitalization due to first episode of schizophrenia or psychotic relapse	Haloperidol/Olanzapine/Risperidone Age (y): 41.8±14.4/37.2±13.1/35.7±13.2 Gender (% male): 81/66/59 Ethnicity: NR	NR NR 323	7 84 273 (1-year follow-up), 219 (2-year follow-up)
Philippe, 2005 France	ICD-10 criteria for schizophrenia and to be between 18 and 64 years old Patients hospitalized for more than 1 year were excluded	Mean age 39.4 years Male 64% Ethnicity NR	NR/NR/3470	NA/NA/3470

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Peuskens 2009 Belgium	294/323 patients (91%) had ≥1 follow-up visit Mean follow-up time of these 294 patients was 597±219 days (haloperidol), 630±186 days (olanzapine), and 640±200 days (risperidone), P=0.026 Haloperidol/Olanzapine/Risperidone Continuation rates (%) after 2 years: ≥1 post-baseline visit: 88/92/92 Completers: 59/66/71 Stable: 47/68/61 Stable completers: 31/50/43 Allocated to treatment group but longer on another drug: 13/10/15 Switches: 39 (1-2 switches per patient)/23 (1-5 switches per patient)/31 (1-4 switches per patient) Of 323 patients, 63% had no antipsychotic treatment switch or addition (stable patients) There were 328 hospitalizations in 150 patients, of which 47 were hospitalized once (15%), and 83 were hospitalized 2-8 times (26%) 165 were never hospitalized (51%); 28 had no follow-up data (9%) Full-time hospitalization (%): 50/44/35 (NS) Time to first rehospitalization (d): 123±168/215±189/209±184 (NS) Duration of full-time hospitalization: 94±166/48±91/55±122 Social status, living environment and employment all remained stable over the 2-year study
Philippe, 2005 France	At baseline, 2.2% of schizophrenic patients in the study cohort already had a diagnosis of diabetes vs.. an age and gender matched sample of the general population (1.5%). Incidence of diabetes from 1993 to 2002 Conventional antipsychotic 2.8% Risperidone 2.4% Olanzapine 2.7% Clozapine 2.1% Amisulpride 2.4%

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Peuskens 2009 Belgium	Haloperidol/Olanzapine/Risperidone Adverse Events Weight gain Mean baseline weight (kg): 79.2±12.5/74.9±13.9/75.3±14.2 Overall weight gain (kg): NR/2.6/2.6 P<0.05 (olanzapine and risperidone) Patients with weight gain >7% (%): 19/29/33 Weight gain of patients who dropped out from study: 1.5±4.1 kg/year Weight gain of patients who remained in study: 1.7±9.0 kg/year 5 patients died	Sample size for haloperidol group was small, plus the group differed from the other groups in marital, institutionalized, and educational status
Philippe, 2005 France	The standard mortality ratio was 3.6 (95% confidence intervals: 3.3 and 4.0), indicating a risk of death for schizophrenic patients in the study between three and four times higher than that of the general population.	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Procyshyn, 1998 Canada	Chart review from Riverview Hospital in British Columbia	Retrospective	6 weeks
Rascati, 2003 United States	Database: Texas Department of Health Medicaid Program	Retrospective	January 1996 through August 1999
Ray, 2009 United States	Computerized files of Tennessee Medicaid	Retrospective	January 1, 1990 through December 31, 2005

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Procyshyn, 1998 Canada	NR	Mean Doses: risperidone: 5.3mg/day vs olanzapine: 14.5mg/day
Rascati, 2003 United States	1 year	olanzapine: 12.87mg/day risperidone 4.40mg/day
Ray, 2009 United States	Median followup of 2.2 years for nonuser of antipsychotic drugs Median 2.9 years for current user	Antipsychotic Drugs vs no use

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Procyshyn, 1998 Canada	Aged ≤ 65 years, schizophrenia or schizoaffective disorder, discharged from hospital or ≥120 days follow-up in hospital, Types of Schizophrenia: catatonic, disorganized, paranoid, undifferentiated, residual, schizoaffective disease, other schizophrenia	Mean Age: 37 years 57.5% Male Ethnicity NR	2339/1901/1345 Risperidone: N=924, Olanzapine: N=977	300/0/1345
Rascati, 2003 United States	Schizophrenia or schizoaffective disorder	Mean age: 41.43 years 53% female 42% Caucasian, 34% African-American, 14% Hispanic, 0.97% Asian, 0.24% Native American, & 8.32% other	NR/NR/2885	NR/NR/2885
Ray, 2009 United States	Persons 30-74 years of age enrolled in Tennessee Medicaid for at least 730 days (gaps of <7 days were allowed) and have been eligible for full pharmacy benefits and made regular use of medical care (defined as having had at least one filled prescription and one outpatient visit in each of the 2 preceding years); at least 1 qualifying day of use of antipsychotic drugs during the study period	Mean age: 45.7 years 34.8% male 70.5% white	NR/NR/186600 nonusers and 93300 current user of antipsychotic drugs at cohort entry	NA/NA/186600 nonusers; 44218 users of typical antipsychotic drugs; 46089 users of atypical antipsychotic drugs

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Procyshyn, 1998 Canada	NR
Rascati, 2003 United States	% who discontinued medication: olanzapine=8.87% risperidone =14.5% Affects on medication choice: Region: Increase likelihood of being prescribed olanzapine by 3% to 5% when in Austin, Lubbock or Dallas vs decreased likelihood by 3% when in San Antonio or Houston Comorbid diagnosis: Having nonorganic mental illness as a comorbid diagnosis decreased likelihood of being prescribed olanzapine by 2% and having diabetes as a comorbid diagnosis also decreased likelihood of being initiated on olanzapine by 3% Previous medication use: for each antipsychotic used in the pre-period the likelihood of being started on olanzapine increased by 3.5%. If an atypical was used in the pre-period the likelihood of being initiated on olanzapine increased by 8% Schizophrenia related costs: History of clozapine use was associated with an increase of $3158 (US) per year History of depot antipsychotic use was associated with an increase of $1645 (US) per year Total health care costs: Previous hospitalization or history of clozapine use was associated with an increase of $3424 (US) per year and $2451 (US) per year, respectively
Ray, 2009 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Procyshyn, 1998 Canada	Number of Patients Discontinued: Due to Side Effects: R: 36(4%) vs O: 23(2%); P=0.70 Number of patients who experienced AE: R: 123(13%) vs O: 109(11%); P=0.20 Body as a whole: R: 8(0.9%) vs O: 13(1.3%); P=0.30 Central and peripheral nervous system: R: 73(7.9%) vs O: 56(5.7); P=0.06 Psychiatric: R: 45(4.9%) vs O: 40(4.1); P=0.40 Gastrointestinal: R: 21(2.3%) vs O: 13(1.3%); P=0.10 Metabolic and nutritional: R: 1(0.1%) vs O: 17(1.7%); P=0.04 Others: 27(2.9%) vs O: 17(1.7%);	
Rascati, 2003 United States	NR	
Ray, 2009 United States	The risk of sudden cardiac death increased with an increasing dose among current users of typical or atypical antipsychotic drugs (given in figure). Users of the typical agents: incidence-rate ratios increased from 1.31 (95% CI, 0.97 to 1.77) for persons taking low doses to 2.42 (95% CI, 1.91 to 3.06) for those taking high doses (P<0.001 for dose–response relationship). Users of the atypical drugs: the incidence-rate ratios increased from 1.59 (95% CI, 1.03 to 2.46) for persons taking low doses to 2.86 (95% CI, 2.25 to 3.65) for those taking high doses (P=0.01 for dose–response relationship).	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Remington, 2001 Canada	Hospital records from the Schizophrenia and Continuing Care Program at the Centre for Addiction and Mental Health	Retrospective	≥18 months (1993-1995)
Ren, 2006 United States	Database: VA National administrative data and VA pharmacy benefits management strategic healthcare group	Retrospective	October 1, 1998 through September 30, 1999
Rettenbacher, 2006 Austria	Laboratory measurements of included subjects	Prospective	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Remington, 2001 Canada	NR	Oral or depot conventional antipsychotic Clozapine Risperidone
Ren, 2006 United States	1 year	Olanzapine Risperidone
Rettenbacher, 2006 Austria	4 weeks	Olanzapine Clozapine Amisulpride Ziprasidone

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Remington, 2001 Canada	Schizophrenia	Oral Conventional/ Depot Conventional/Clozapine/ Risperidone Mean age (years): 31.7/36.5/33.4/31.7 % male: 55/55/66/53	314/66/66	NR/NR/NR
Ren, 2006 United States	Schizophrenia either paranoid type, disorganized type, catatonic type, undifferentiated type, residual type, schizophreniform disorder or schizoaffective disorder	Olanzapine/Risperidone: Mean age (years)=50/50.5 % male=94.7/94.7 % Caucasian=43.7/43.9 % African-American=31.5/33.9 % Hispanic=6.9/4.7 % other ethnicity=17.9/17.6	NR/NR/7144	NR/NR/NR
Rettenbacher, 2006 Austria	Schizophrenia	Age range: 18-65 years	NR/NR/NR	NR/NR/35

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Remington, 2001 Canada	No significant differences were found between groups for number of hospital visits, days in hospital, or emergency room visits. Clozapine takers had a higher number of doctor visits compared to those taking either form of conventional antipsychotic, while risperidone takers had a higher number of doctor visits compared only to those taking oral conventional antipsychotics. CGI scores were significantly improved over the 18 months for those treated with clozapine, risperidone, and depot conventional antipsychotics versus oral conventional antipsychotics.
Ren, 2006 United States	Incidence of comorbid conditions: Those initiated on risperidone had more overall comorbid conditions (2.79 vs 2.68; P<0.05) and more medical comorbid conditions (1.53 vs 1.44; P<0.05) than olanzapine initiators Incidence of concomitant medications Those initiated on olanzapine used more mood stabilizers (14.45% vs 12.42%; P<0.05) and more overall number of drugs for psychiatric conditions (0.78 vs 0.73; P<0.05) than risperidone Incidence of hospitalizations No difference was found between the treatment groups regarding individuals having at least one psychiatric hospitalization Incidence of discontinuation Initiating with olanzapine decreased the incidence of discontinuation by 12%, when adjusted for sociodemographic and clinical information
Rettenbacher, 2006 Austria	No significant differences were found between clozapine and olanzapine-treated patients regarding changes in scores of BMI and serum lipids (P>0.2).

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Remington, 2001 Canada	NR	
Ren, 2006 United States	NR	
Rettenbacher, 2006 Austria	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Ritsner, 2006 Ritsner, 2004 Israel	Sha'ar Menashe Mental Health Center Case Register	Prospective	NR
Sax, 1998 United States	University of Cincinnati Medical Center site	Prospective	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Ritsner, 2006 Ritsner, 2004 Israel	1 year	Olanzapine 15.2 mg/day Risperidone 4.4mg/day Typical antipsychotics mean dose NR
Sax, 1998 United States	6 weeks	quetiapine 330mg 6 weeks

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Ritsner, 2006 Ritsner, 2004 Israel	Schizophrenia diagnosed based on DSM-IV criteria; age 18-60 years	ITT population: Mean age=39.6 years 76.7% male Race NR PP population (n=124) Mean age=40.0 years 78.2% male Race NR	150/136/133	9 (6.8%) withdrawn 4 (3%) lost to fu 124 analyzed
Sax, 1998 United States	Schizophrenia	Mean age=32 70% male 80% Caucasian	NR/NR/10	NR/NR/10

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Ritsner, 2006 Ritsner, 2004 Israel	**Q-LES-Q index** (% change from baseline estimated from Figure 2): risperidone= +3.5% vs olanzapine= +14% vs first-generation agents= +6% vs combined therapy= -4%; 2-way ANCOVA test of treatment group effect: F=3.1, p=0.029; effect size for risperidone vs olanzapine= -0.57 **Physical health index** (% change estimated from Figure 2): risperidone= +5% vs olanzapine= +17% vs first-generation agents= +14% vs combined therapy= -2%; 2-way ANCOVA test of treatment group effect: F=2.1, p=0.15; effect size for risperidone vs olanzapine= -0.51 **Subjective feelings** (% change estimated from Figure 2): risperidone= +9.5% vs olanzapine= +20% vs first-generation agents= +7.5% vs combined therapy= -2%; 2-way ANCOVA test of treatment group effect: F=2.7, p=0.050; effect size for risperidone vs olanzapine= -0.29 **Leisure time activities** (% change estimated from Figure 2): risperidone= +13% vs olanzapine= +20.5% vs first-generation agents= +4% vs combined therapy= -2%; 2-way ANCOVA test of treatment group effect: F=3.2, p=0.026; effect size for risperidone vs olanzapine= -0.18 **Social relationships** (% change estimated from Figure 2): risperidone= +6% vs olanzapine= +14% vs first-generation agents= +8% vs combined therapy= +0.5%; 2-way ANCOVA test of treatment group effect: F=0.6, p=0.64; effect size for risperidone vs olanzapine= -0.28 **General activity** (% change estimated from Figure 2): risperidone= -3% vs olanzapine= +6% vs first-generation agents= +3.5% vs combined therapy= +4%; 2-way ANCOVA test of treatment group effect: F=0.3, p=0.84; effect size for risperidone vs olanzapine= -0.52 **Life satisfaction** (% change estimated from Figure 2): risperidone= +3.5% vs olanzapine= +26.5% vs first-generation agents= +22% vs combined therapy= +2%; 2-way ANCOVA test of treatment group effect: F=0.2, p=0.88; effect size for risperidone vs olanzapine= -0.42
Sax, 1998 United States	Patients(n=10) vs Controls(n=12) CPT sensitivity, mean (SD) initial: 0.82(0.10) vs 0.93(0.07), p<0.01 first follow up: 0.88(0.08) vs NA second follow up: 0.92(0.07)* vs 0.94(0.08) (*p<0.01 vs baseline) No significant correlations between changes in symptom scores and CPT performance results, or between dosage of quetiapine and CPT and BPRS changes over time.

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Ritsner, 2006 Ritsner, 2004 Israel	NR	
Sax, 1998 United States	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Schillevoort, 2001 Netherlands	PHARMO-database	Retrospective	90 days
Schillevoort, 2001b Netherlands	PHARMO-database	Retrospective	90 days
Sernyak, 2002 United States	Veterans Health Administration of the Department of Veterans Affairs (VA)	Retrospective	October 1, 1999 to September 30 1999
Shajahan, 2009, Scotland	Chart Review: Lanarkshire, Scotland	Retrospective	2002-2007
Sharif, 2000 United States	Creedmoor Psychiatric Center, Columbia University	Retrospective	12 weeks
Snaterse, 2000 Canada	Alberta Hospital Edmonton	Retrospective	12 months

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Schillevoort, 2001 Netherlands	NR	haloperidol: 2.2 mg/d, risperidone: 54 mg/d, olanzapine mg/d
Schillevoort, 2001b Netherlands	NR	Median doses risperidone: 2.0 mg/day haloperidol: 2.2 mg/day zuclopenthixol: 6.0 mg/day perphenazine: 5.3 mg/day thioridazine: 48 mg/day pipamperone: 40 mg/day chlorpromazine: 63 mg/day
Sernyak, 2002 United States	4 months	Clozapine, olanzapine, risperidone, quetiapine
Shajahan, 2009, Scotland	≤5 years	Aripiprazole (N=89): starting dose: 10.2 mg/day, max dose 18.7 mg/day; Quetiapine (N=132): starting dose 91 mg/day, max dose 422 mg/day
Sharif, 2000 United States	4 weeks	Clozapine: 520 mg/day Risperidone: 7.5 mg/day
Snaterse, 2000 Canada	12 months	Risperidone(N=35): 4.17 mg/day Olanzapine(N=21): 15.24 mg/day

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Schillevoort, 2001 Netherlands	Schizophrenia	Mean age: 35.3 years 48.6% Male Ethnicity NR	450,000/NR/848	0/0/848
Schillevoort, 2001b Netherlands	Schizophrenia	Mean age: 36 years 45.9% Male Ethnicity NR	450,000/4094/4094	0/0/4094
Sernyak, 2002 United States	Patients prescribed to study drugs	Mean age: 52.6 years 5.2% Female African-American: 25% Hispanic: 4.3%	NR/NR/38,632	NR/NR/38,682
Shajahan, 2009, Scotland	Diagnosed schizophrenia and related psychoses, onset of treatment with either drug after 2002, and more than one mental health contact	Mean age (Aripiprazole/Quetiapine): 39.6 years/36.7 years; % Male (Aripiprazole/Quetiapine): 58%/52%; Ethnicity: NR	NR/22000/221	NR NR 221 (89 aripiprazole, 132 quetiapine)
Sharif, 2000 United States	Schizophrenia, schizoaffective disorder	Mean age: 35.9 years 54% Male White: 63% Black: 21% Hispanic: 13% Asian: 4%	NR/NR/24	NR/NR/24
Snaterse, 2000 Canada	Schizophrenia, schizoaffective disorder	Mean age: 38.8 years 40.5% Female Ethnicity NR	NR/NR/56	NR/NR/56

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Schillevoort, 2001 Netherlands	NR
Schillevoort, 2001b Netherlands	NR
Sernyak, 2002 United States	Analysis of Association Between Atypicals vs Typicals: 95% CI; p-value clozapine: 1.07-1.46; P<0.005 olanzapine: 1.04-1.18; P<0.002 quetiapine: 1.11-1.55; P<0.002 risperidone: 0.98-1.12; P=0.15
Shajahan, 2009, Scotland	Medication discontinuation rates (Aripiprazole/Quetiapine): 45%/42% ; Time to discontinuation (Aripiprazole/Quetiapine): 103 days/175 days
Sharif, 2000 United States	Patients classified as responders to treatment: clozapine: 14(58%) vs risperidone: 6(25%) Response rates: Positive symptoms: clozapine: 38% vs risperidone: 17% Negative symptoms: clozapine: 29% vs risperidone: 8% Aggressive symptoms: clozapine: 71% vs risperidone: 41%
Snaterse, 2000 Canada	Time to initial response: R: 14.3 days vs O: 30.9 days; P<0.00001 Time to discharge: R: 36.6 days vs 58.2 days; P=0.0201

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Schillevoort, 2001 Netherlands	Use of antiparkinsonian medication at baseline: R: 36.2% vs O: 40.3% vs H: 4.5%; p<0.001No significant differences found at endpoint for use of antiparkinsonian medication with antipsychotic	
Schillevoort, 2001b Netherlands	Crude relative risk for anticholinergic medication (95% CI): risperidone vs haloperidol: 0.44 (0.20, 1.01) risperidone vs zuclopenthixol: 0.49 (0.21, 1.13) risperidone vs perphenazine: 1.92 (0.74, 5.01) risperidone vs thioridazine: 3.12 (1.21, 8.04) risperidone vs pipamperone: 4.25 (1.54, 11.72) risperidone vs chlorpromazine: 2.97 (0.35, 24.97)	
Sernyak, 2002 United States	NR	
Shajahan, 2009, Scotland	NR	
Sharif, 2000 United States	Response rates: Clinical Global Impressions-Improvement scores ≤2: Global rating: R: 25% vs C: 58% Positive symptoms: R: 17% vs C: 38% Negative symptoms: R: 8% vs C: 29% Aggressivity: R: 41% vs C: 71%	
Snaterse, 2000 Canada	Re-admission rate at 12 months: R: 31.4% vs O: 61.9%; P=0.026	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Soholm, 2003 Denmark	Patient records from the Psychiatric University Clinic, Rigshospitalet, Copenhagen University Hospital, Denmark	Retrospective	>1997
Soyka, 2005 Germany (inpatients)	Psychiatric Hospital of the University of Munich Non-randomized, comparative	Prospective	Current hospitalization time (weeks), risperidone vs haloperidol: 6.8 vs 6.2 weeks
Spivak, 1998 Israel	Naturalistic: Ness-Ziona Mental Health Center	Prospective	1 year
Strassnig, 2007 United States	Subset of data from larger ongoing trial	Unclear	1990-2006

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Soholm, 2003 Denmark	NR	1st line of treatment: conventional antipsychotic or clozapine 2nd line of treatment: atypical antipsychotic
Soyka, 2005 Germany (inpatients)	NR	Average dose /d Risperidone: 4.6 mg/d Haloperidol: 10.4 mg/d
Spivak, 1998 Israel	NR	Clozapine 295 mg CAPD (chlorpromazine equivalent) 348.9 mg
Strassnig, 2007 United States	1 year	Classic and novel antipsychotics

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Soholm, 2003 Denmark	Schizophrenia, schizotypal disorder, or schizoaffective disorder	Mean age (years): 38.7 % male: 63	NR/71/57	NR/NR/57
Soyka, 2005 Germany (inpatients)	Schizophrenia or schizoaffective disorder	Mean age: 32.95y 67.5% male Ethnicity: NR	NR/ NR/ 59	NR/ NR / 59
Spivak, 1998 Israel	Treatment resistant schizophrenia	Mean age=38.3 48.3% male Race NR	NR NR 60	NR NR 60
Strassnig, 2007 United States	First-episode psychotic episode	Subjects/Controls Mean age (years): 27.2/21.3 % male: 69.8/61.5	NR/NR/NR	NR/NR/98 subjects & 30 controls

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Soholm, 2003 Denmark	Significantly more individuals were in the olanzapine group than in the risperidone group (P=0.0001) Most common diagnosis of individuals was schizophrenia 67% of those treated with newer atypical antipsychotics as the first line of treatment, stayed on treatment for the duration Those taking olanzapine had significantly fewer days in the hospital (P=0.001)
Soyka, 2005 Germany (inpatients)	Driving ability tests (all subjects had licenses), risperidone vs haloperidol vs control: Psychomotor test performance (no p-values given): passed: 35% vs 5% vs 85% low performance: 40% vs 35% vs 15% very low performance: 25% vs 60% vs 0% Number of pts who failed in each test, risperidone vs haloperidol vs control: PVT (peripheral vision test with tracking task, incl. reaction time): 5 vs 13 vs 0 TT15 (tachistoscope test, ability to quickly extract relevant info):1 vs 4 vs 0 Q1 (attention test under a monotonous condition): 7 vs 11 vs 2 RST3 (reactive stress tolerance test): 11 vs 16 vs 1 Mean BPRS at examination: risperidone=28 vs haloperidol=27.4 (p=NS)
Spivak, 1998 Israel	NR
Strassnig, 2007 United States	Weight Changes Patients on antipsychotics experienced significantly more weight gain during the 1-year observation period and their body mass index increased to a significantly greater extent than their healthy controls (P=0.002) More weight gain was experienced by younger subjects (P=0.019)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Soholm, 2003 Denmark	No significant differences were found between groups for adverse effects. The severity of extrapyramidal symptoms was generally reduced in all groups.	
Soyka, 2005 Germany (inpatients)	NR	Tests are relevant to the German Road Traffic Safety Board.
Spivak, 1998 Israel	Suicide Attempts 0 vs 5 (16.7%); p<0.05	
Strassnig, 2007 United States	Side-effect medications were prescribed more often for those taking haloperidol and perphenazine	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Strous, 2006 Israel	Clinic visits	Prospective	NR
Su, 2005 Taiwan	Clinic visits	Prospective	NR
Sumiyoshi, 2004 United States	Outpatient community mental health center (Mental Health Cooperative at Nashville, TN)	Prospective (with retrospective epidemiologic survey of clinical and demographic information)	February 2001 to May 2002
Swanson, 2004 United States	Medical records from the North Carolina site of the Schizophrenia Care and Assessment Program	Retrospective	1997 to 1999
Taylor, 2003 UK	U.K. Risperidone Olanzapine Drug Outcomes Studies in Schizophrenia program (RODOS-UK)	Retrospective	4 months

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Strous, 2006 Israel	12 weeks	Risperidone, olanzapine, clozapine
Su, 2005 Taiwan	3 months	Olanzapine 7.9mg, risperidone 2.5mg
Sumiyoshi, 2004 United States	NR	Clozapine, Risperidone, Olanzapine or Quetiapine
Swanson, 2004 United States	3 years	Olanzapine Risperidone
Taylor, 2003 UK	NR	risperidone: 5.5±2.4 mg/day olanzapine: 14.1±4.7 mg/day

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Strous, 2006 Israel	Schizophrenia or schizoaffective disorders	Mean age=36.7 58.0% male Race NR	NR/NR/131	0/0/131
Su, 2005 Taiwan	DSM-IV criteria for schizophrenia; poor or partial response to current antipsychotic (olanzapine or risperidone) for at least 3 months	Mean age=35.7 53% male Ethnicity NR	NR/30/15	NR/NR/15
Sumiyoshi, 2004 United States	Patients who visited the mental health center during the sampling frame and if he or she was receiving clozapine, risperidone, olanzapine or quetiapine 46.6% diagnosed with schizophrenia spectrum disorders	Mean age (SD): 42.9 (10.6) years 56.9% male 60.3% white; 39.7% non-white	NR/NR/116	NR/NR/116
Swanson, 2004 United States	Schizophrenia-related disorders	Mean age (years): 46.1 % male: 56 % African-American: 67.7	NR/NR/124	NR/NR/124
Taylor, 2003 UK	Schizophrenia, schizoaffective disorder	Mean age: 36.2 years 68.5% male Ethnicity NR	NR/NR/501	NR/NR/499

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Strous, 2006 Israel	NR
Su, 2005 Taiwan	NR
Sumiyoshi, 2004 United States	NR
Swanson, 2004 United States	Olanzapine takers had a reduced probability of violence over time Trend toward greater compliance with medication among those who remained on olanzapine therapy for ≥ 12 months (OR=1.94, p=0.07)
Taylor, 2003 UK	% of effectiveness: R: 78% vs O: 74%; P=.39 Mean time to onset of effectiveness: R: 17.6 days vs O: 22.4 days; P=.01 Mean days in hospitalization: R: 58 days vs R: 49 days; P=.007

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Strous, 2006 Israel	Proportional increase in weight: Clozapine=6.9% Olanzapine=2.7% Risperidone=2.1% 2x3x2 ANOVA results (gender and group as between-subjects and time as within subjects factors): F(2,128)=8.52, p<0.0001 Post-hoc Tukey-HSD 2x2 comparisons: Clozapine vs olanzapine (p<0.05) and vs risperidone (p<0.05)	
Su, 2005 Taiwan	Change in Mean Body Weight in kg: Baseline/endpoint (% change) Olanzapine (after switch from risperidone): 70.1/66.1 (-6%), p=0.049 Risperidone (after switch from olanzapine): 65.9/69.9 (+6%), p=0.008 Change in BMI: Baseline/endpoint (% change) Olanzapine (after switch from risperidone): 25.7/24.2 (-6%), p=0.04 Risperidone (after switch from olanzapine): 24.8/25.9 (+4%), p=NS	
Sumiyoshi, 2004 United States	Nonparametric survival analysis indicated no statistically signifcant difference in time to onset of type 1 and type 2 diabetes mellitus between clozapine (median: 112 days; mean (SD): 495.6 (738.4) days), risperidone (median: 502 days; mean (SD): 789.8 (829.9) days), and olanzapine (median: 399 days; mean (SD): 602.8 (574) days). *P*=0.43	
Swanson, 2004 United States	NR	
Taylor, 2003 UK	% of patients discontinued due to side effects: R: 3.7% vs O: 2.3% Events reported: body as a whole, central/peripheral nervous system, psychiatric, gastrointestinal, metabolic/nutritional, heart rate/rhythms	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Taylor, 2006 UK- Scotland	Not reported	Prospective	2002 plus 6 month follow-up
Taylor, 2008, Scotland	Case record review: Lankshire, Scotland	Retrospective	February 2002-June 2005
Tiihonen, 2006 Finland	Community care	Prospective	1996-2001

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Taylor, 2006 UK- Scotland	6 months	At 6 months mean doses were amisulpride (n=16) 487.5mg, for clozapine (n=12) 429 mg, for olanzapine (n=65) 13.7 mg, for quetiapine (n=8) 350 mg, and for risperidone (n=56) 3.4 mg.
Taylor, 2008, Scotland	NR	Mean Dose for Schizophrenia (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 589/15.5/441/6.0/427 mg/d
Tiihonen, 2006 Finland	3.6 years	Olanzapine, clozapine, risperidone, oral perphenazine, thioridazine, perphenazine depot, chlorprothixene, chlorpromazine, haloperidol, and levomepromazine

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Taylor, 2006 UK- Scotland	All patients from adolescent, adult, and old age psychiatry in the Greater Glasgow area (population -1.0 million) with a clinical diagnosis (from a senior psychiatrist) of schizophrenia or schizophreniform disorder.	Mean age 45.9 years 51% male Ethnicity- NR	NR study started with 373 patients	81/ NR/ 101
Taylor, 2008, Scotland	Schizophrenia or related psychoses (aged 16-65), and initiation of treatment with SGAs after EPR reviews commenced	Mean age (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 41/40/41/43/37 years; % Male (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 63/64/38/62/65%; Ethnicity: NR	NR 11250 1464	NR NR 1464
Tiihonen, 2006 Finland	All people in Finland who were hospitalized because of a diagnosis of schizophrenia or schizoaffective disorder; index ages 15-45 years	Mean age 30.7 years 62% male Ethnicity or race NR	NA- all were included that were hospitalized in Finland	0/0/2230

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Taylor, 2006 UK- Scotland	Mean change from baseline and % change CGI Amisulpride 0.85 19% Clozapine 1.80 34% Olanzapine 1.18 33% Quetiapine 0.83 11% Positive symps Amisulpride 0.55 30% Clozapine1.50 54% Olanzapine 0.9 51% Quetiapine 0.67 26% Negative symps Amisulpride 0.40 24% Clozapine 0.40 20% Olanzapine 0.26 11% Quetiapine 1.00 39% Side effects, Amisulpride 0.87 54% (1.5) Clozapine 0.10 13% Olanzapine 0.90 51% Quetiapine 1.50 53% Quality of life, Amisulpride 0.38 15% Clozapine 1.10 34% (1.7)Olanzapine 0.96 36% Quetiapine 1.17 31%
Taylor, 2008, Scotland	Medication discontinuation rates (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 51/41/36/28/18%; Adjusted discontinuation rates (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 0.71/0.64/0.54/0.53/0.25; Medication discontinuation rate due to side effects (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 35/32/46/0/14%; Medication discontinuation rate due to inefficacy (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 33/28/36/73/0%; Medication discontinuation rate due to 'other' (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 32/40/18/27/86%; Mean number of days to discontinuation (Amisulpride/Olanzapine/Quetiapine/Risperidone/Clozapine): 232/256/191/152/427 days
Tiihonen, 2006 Finland	Hospitalization- Drug and crude RR/adjusted RR (sex, calendar year, age at onset of follow-up, number of previous relapses, duration of index hospitalization, and length of follow-up) Perphenazine depot 0.54 (0.41 to 0.70) 0.54 (0.41 to 0.70) Clozapine 0.79 (0.66 to 0.95) 0.64 (0.53 to 0.77) Olanzapine 0.81 (0.67 to 0.97) 0.67 (0.56 to 0.80) Thioridazine 0.73 (0.59 to 0.91) 0.75 (0.60 to 0.93) Perphenazine oral 0.66 (0.54 to 0.80) 0.77 (0.63 to 0.94) Chlorpromazine 0.83 (0.66 to 1.04) 0.89 (0.71 to 1.12) Chlorprothixene 0.85 (0.68 to 1.06) 0.90 (0.72 to 1.13) Mixed or rare 1.05 (0.89 to 1.25) 0.91 (0.76 to 1.08) Haloperidol oral 1.00 1.00 Levomepromazine 1.53 (1.22 to 1.93) 1.01 (0.80 to 1.27) Risperidone 0.89 (0.74 to 1.06) 0.87 (0.73 to 1.05)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Taylor, 2006 UK- Scotland	NR	
Taylor, 2008, Scotland	NR	Max doses were not reported but results were discussed
Tiihonen, 2006 Finland	84 patients died during follow-up, no significant differences between drugs but, mortality was more than 10 times higher in patients not taking drugs than in patients currently taking antipsychotic drugs: 75 patients not taking drugs died (3362 person years) and nine patients taking drugs died (4664 person years) (adjusted relative risk 12.3) Twenty six suicides occurred in patients not taking drugs compared with one suicide in patients taking drugs (crude relative risk 36.1, 4.9–266)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Tiihonen, 2009 Finland	National Hospital Discharge Register	Retrospective	January 1, 1996 to 2006 (because prescription data are available only after 1995)
Usall, 2009 SOHO (Secondary publication) Reporting on gender differences in Schizophrenia	Same as Haro 2005	Same as Haro 2005	6 month analysis
van Winkel, 2008, Belgium	University Psychiatric Center of the Katholieke Universiteit Leuven in Kortenberg, Belgium	Prospective	November 2003-January 2007

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Tiihonen, 2009 Finland	11-year follow-up with average of 8.6 years	First generation and second generation antipsychotic drugs either as monotherapy or combinations, as well as no therapy
Usall, 2009 SOHO (Secondary publication) Reporting on gender differences in Schizophrenia	NR	Male vs female Olanzapine: 11.08 (5.37) vs 10.19 (4.99) Risperidone: 4.67 (2.57) vs 4.09 (2.54) Clozapine: 159.68 (125.03) vs 148.01 (125.63)
van Winkel, 2008, Belgium	3 months	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Tiihonen, 2009 Finland	All patients in Finland who were admitted with a diagnosis of schizophrenia from Jan 1, 1973, to Dec 31, 2004	Mean age: 51 years 46.1% male	NA: all patients in Finland admitted with a diagnosis of schizophrenia	NA/NA/66881
Usall, 2009 SOHO (Secondary publication) Reporting on gender differences in Schizophrenia	Schizophrenia	age: 39.7 % male: 56.7 Ethnicity: NR	NR/NR/7990	NR/NR/7990
van Winkel, 2008, Belgium	Patients with schizophrenia or schizoaffective disorder, newly started on or switched to specific atypical antipsychotic medication therapy, with OGTT-confirmed non-diabetic status	Mean age: 33.7 years; % Male: 60.7%; Ethnicity: NR	NR/415/183	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Tiihonen, 2009 Finland	NR
Usall, 2009 SOHO (Secondary publication) Reporting on gender differences in Schizophrenia	Overall CGI response Odds ratio for gender [Female reference category], 95% CI, p-value Olanzapine: 0.88 (0.78 to 1.00), p=0.0460 Risperidone: 0.90 (0.74 to 1.10), p=0.2969 Clozapine: 0.56 (0.34 to 0.93), p=0.0252 Typical cohort: 0.62 (0.48 to 0.82), p=0.0006 EQ-VAS change from baseline, differences in rating by gender (female reference category) Olanzapine: -1.52(-2.53 to -0.50), p=0.0033 Risperidone: 0.27 (-1.28 to 1.83), p=0.7300 Clozapine: -2.03 (-6.06 to 2.00), p=0.3243 Typical cohort: -2.16 (-4.33 to 0.01), p=0.0505
van Winkel, 2008, Belgium	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Tiihonen, 2009 Finland	Overall risk of death was lower during the current use of any antipsychotic drug than it was with no antipsychotic use; adjusted HR, 0.68; 95% CI, 0.65 to 0.71; *P*<0.0001). Risk of death significantly lower in patients with long term (7-11 years) antipsychotic treatment than in those who had not used any antipsychotic drugs during follow-up; HR, 0.81; 95% CI, 0.77 to 0.84; *P*<0.0001) Life expentancy of patients with schizohrenia had not declined during the study period compared with the general population (32.5 years vs 57.5 years in 1996 respectively; 37.4 years vs 59.9 years in 2006 respectively)	
Usall, 2009 SOHO (Secondary publication) Reporting on gender differences in Schizophrenia		
van Winkel, 2008, Belgium	8 patients developed diabetes within 3 months after the start of the atypical antipsychotic, resulting in a 3-month incidence rate of 4.4% . Initiation of clozapine 9.5% of patients initiated on clozapine, 8.0% of patients initiated on olanzapine, 4.2% of patients initiated on quetiapine, and 2.1% of patients initiated on risperidone developed new-onset diabetes, whereas no new cases developed in patients initiated on aripiprazole and amisulpride. 5 of the 8 (62.5%) had prediabetic abnormalities at baseline; 3 (37.5%) had no glucose abnormalities. Type of initiation (start or switch) did not affect the metabolic parameters. BMI (kg/m^2)at baseline and after 3 months: amisulpride = 26.5, 27.9 aripiprazole = 28.4, 27.3 clozapine = 24.8, 26.5 olanzapine = 23.5, 25.8 quetiapine = 25.2, 26.8 risperidone = 24.9, 25.8	Sample size (183) was small for assessing the low incidence rates typically reported for diabetes. Study was naturalistic: there was no random allocation of antipsychotic medication which resulted in treatment cohorts of different sizes.

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Verma, 2001 United States	Houston VA Medical Center	Retrospective	Average: 25 days

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Verma, 2001 United States	NR	risperidone: 2.2 mg olanzapine: 13.2 mg

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Verma, 2001 United States	Schizophrenia	Mean age: 71.4 years 100% male 71% Caucasian, 23% African-American, 6% Hispanic	NR/NR/NR	NR/NR/34

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Verma, 2001 United States	Changes in scores at discharge: Positive and negative symptoms (PANSS): R: 56.90 vs O: 59.0; P=0.735 Extrapyramidal side-effect rating scale (ESRS): R: 23.46 vs O: 20.54; P=0.557 Rating scale for side effects (RRSE): R: 8.14 vs O: 7.71; P=0.817

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Verma, 2001 United States	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Voruganti, 2000 Voruganti, 2002 Canada	Western Ontario schizophrenia research program	Retrospective	NR
Wang, 2002 U.S.	Databases: NJ Medicaid program & NJ Pharmaceutical Assistance to the Aged & Disabled program plus Medicare	Retrospective	6 months before date of 1st prescription for insulin or oral hypoglycemic agent

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Voruganti, 2000 Voruganti, 2002 Canada	≥6 months	Risperidone(N=50): 2-8 mg Olanzapine(N=50): 15-40 mg Quetiapine(N=50): 200-800 mg Switched from following conventional drugs (CAPD): chlorpromazine, fluphenazine, flupenthixol, haloperidol, methotrimeprazine, perphenazine, pimozide, Pipothiazine, trifluoperazine
Wang, 2002 U.S.	6 months	clozapine vs other psychiatric agents (includes typical APs and risperidone); Dose and duration of treatment during the 6-month observation period were included in the analysis

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Voruganti, 2000 Voruganti, 2002 Canada	Schizophrenia	Mean age: 32.1 years 68.7% male	NR/230/150	15 withdrawals or lose to follow up/135
Wang, 2002 U.S.	Patients with psychiatric disorders, age>20, enrolled in government-sponsored drug benefit programs in New Jersey. Cases were patients with a 1st prescription (index date) for insulin or oral hypoglycemics between 1990-1995. Controls were patients without diabetes, matched on age, gender, and a randomly assigned index date. Subjects were then selected for analysis if they had a psychiatric diagnosis in the previous 6 months.	Mean age 62.5 31.8% male 64% white	NR NR 14007	NR NR 14007 analyzed Cases with diabetes mellitus n=7227 Controls without diabetes mellitus n=6780

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Voruganti, 2000 Voruganti, 2002 Canada	85% of patients benefitted from switching from conventional to novel antipsychotics 8(6%) preferred conventional treatment Remained on maintenance treatment: risperidone 82% olanzapine 86% quetiapine 82% CAPD (n=44) vs risperidone (n=50) vs olanzapine (n=48) vs quetiapine (n=42) vs clozapine (n=46) Psychosocial functioning and quality of life: Sickness impact profile (SIP): 35.3(13.2)* vs 26.9(14.3) vs 29.1(14.8) vs 28.2(10.6) vs 32.1(18.1) Quality of life (QLS): 58.8(22.6) vs 63.3(15.3) vs 60.8(15.4) vs 61.4(14.2) vs 58.2(14.8) Global assessment of functioning scale (GAF): 59.8(14.5) vs 61.9(10.5) vs 59.4(8.9) vs 56.8(12.6) vs 57.8(10.6) (*p<0.05 on Tukey tests) Mean change in scores after a switch from conventional to the novel antipsychotic drugs risperidone (n=43) vs olanzapine (n=44) vs quetiapine (n=31) Symptoms 1. PANSS: -23.63 vs -23.67 vs -21.43 a. positive symptoms cluster: -5.18 vs -4.11 vs -4.67 b. negative symptoms cluster: -8.2* vs -6.3 vs -5.0 c. excited symptoms cluster: -3.68 vs 2.79 vs -1.03 d. depressive symptoms cluster: 2.68 vs -6.09* vs -1.70 e. cognitive symptoms cluster: -3.89 vs -4.38 vs -9.03* Quality of life 1. QLS: 10.30 vs 9.97 vs 9.87 2. GAF: 16.0 vs 15.18 vs 14.67 3. SIP: -22.32 vs -20.40 vs -21.20 (*p<0.05 on post hoc Tukey tests)
Wang, 2002 U.S.	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Voruganti, 2000 Voruganti, 2002 Canada	CAPD (n=44) vs risperidone (n=50) vs olanzapine (n=48) vs quetiapine (n=42) vs clozapine (n=46) Drug attitude inventory scores: 1. DAI-30 total: 12.9(10.5) vs 19.4(9.1)* vs 18.9(8.9)* vs 18.2(10.2)* vs 16.2(11.0) 2. subjective positive: 3.1(4.2) vs 5.4(3.3)* vs 5.5(2.7)* vs 5.8(3.8)* vs 4.9(3.6) 3. subjective negative: 2.4(3.5) vs 3.2(2.8) vs 3.5(2.5) vs 2.7(3.2) vs 2.4(3.3) 4. health/illness: 1.7(1.1) vs 1.7(1.8) vs 1.6(1.6) vs 1.5(1.2) vs 1.2(1.9) 5. professionals: 1.6(0.9) vs 1.7(0.7) vs 1.1(1.5) vs 1.6(0.9) vs 1.5(1.0) 6. control issues: 0.6(1.3) vs 1.4(1.1) vs 1.3(1.2) vs 0.9(1.2) vs 1.2(1.2) 7. prevention: 1.1(1.0) vs 1.6(0.9) vs 1.3(1.2) vs 1.5(1.1) vs 1.4(1.7) 8. harmful effects: 0.4(1.3) vs 0.9(1.3) vs 0.9(1.2) vs 0.8(1.0) vs 0.6(1.5) Proportion of dysphoric responders:7(17%)* vs 3(6%) vs 2(5%) vs 3(7%) vs 3(6.5%) Severity of side effects 1. Simpson-Angus EPS rating scale: 3.4(2.3)* vs 1.34(2.4) vs 0.9(2.0) vs 1.1(2.2) vs 0.4(1.4) 2. BAS: 1.2(1.4) vs 0.8(0.9) vs 0.2(0.6) vs 1(1.2) vs 0.6(1.0) 3. AIMS: 1.6(2.1) vs 1.2(2.4) vs 1.4(2.8) vs 1.2(3.2) vs 3.5(5.8) 4. LUNSERS: 21.1(9.6)* vs 13.4(9.4) vs 13.4(4.0) vs 12.8(7.2) vs 25.4(15.7)* (*p<0.05 on Tukey tests) Mean change in scores after a switch from conventional to the novel antipsychotic drugs risperidone (n=43) vs olanzapine (n=44) vs quetiapine (n=31) Side effects 1. AIMS: -0.21 vs -0.75 vs -0.12 2. BAS: 3.40 vs -4.52 vs -3.96 3. SAS: -6.02 vs -6.75 vs -6.67 4. LUNSERS: -21.86 vs -23.18 vs -30.7* Subjective tolerability: 1. DAI: 11.86 vs 14.6* vs 12.12 2. proportion of dysphoric responders in the group (%): -6.9 vs -13.6 vs -9.7 (*p<0.05 on post hoc Tukey tests)	
Wang, 2002 U.S.	Adjusted odds of diabetes mellitus associated with clozapine use: 0.98 (95% CI 0.74-1.31) Adjusted odds of DM associated with use of other antipsychotics: 1.13 (95% CI 1.05-1.22) Adjusted odds of DM associated with specific antipsychotics (95% CI): risperidone 0.90 (0.96-1.18) chlorpromazine 1.31 (1.09-1.56) perphenazine 1.34 (1.11-1.62) haloperidol 1.06 (0.96-1.18)	Duration of treatment and previous treatment with clozapine, prior to the 6-month window of observation were not included in the analysis.

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Weiser, 2000 Israel	Tel-Aviv University Medical School	Retrospective	NR
Wirshing, 2002 United States	VA Greater Los Angeles Healthcare System	Retrospective	Mean duration: clozapine: 43.3 mo olanzapine: 13.5 mo risperidone: 28.6 mo quetiapine: 33.o mo haloperidol: 37.1 mo fluphenazine: 47.0 mo
Yood, 2009 U.S.A.	3 sites: Kaiser Permanente Health Plan, Northern California; HealthCore Integrated Research Network; PharMetrics	Retrospective	Nov 2002 through March 2005

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Weiser, 2000 Israel	NR	Haloperidol(N=23): 10 mg/day Olanzapine(N=26): 10.56 mg/day Risperidone(N=27): 4.35 mg/day
Wirshing, 2002 United States	NR	Clozapine, olanzapine, risperidone, quetiapine, haloperidol, fluphenazine/mean doses NR
Yood, 2009 U.S.A.	minimum 45 days	% of inception cohort (N=56,037) Aripiprazole 4.5% Clozapine 0.1% Olanzapine 22.2% Quetiapine 18.2% Risperidone 19.6% Ziprasidone 2.9% Typical antipsychotics 10.5% Mean dose NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Weiser, 2000 Israel	Schizophrenia, schizophreniform disorder	Mean age: 30.9 years 68% Male Ethnicity NR	NR/NR/NR	NR/NR/76
Wirshing, 2002 United States	Schizophrenia	Mean age: 51.3 years 94.4% Male 47.9% White 36.7% African-American	NR/590/215	0/0/215
Yood, 2009 U.S.A.	Inception cohort subset: all patients aged 18 and older exposed to typical or atypical antipsychotics for at least 45 days and continuously enrolled in the database for at least 3 months before and 6 months after the index date with no evidence of diabetes anytime before the index date, and no previous antipsychotic prescription filled within 3 months before the index date.	Mean (SD) age: 45.1 (19.4) 39.7% male Ethnicity NR	77946 = simple cohort 56037 eligible as inception cohort All eligible were included in analysis.	No withdrawals, no loss to followup: subjects selected based on continuous enrollment for 6 months after index date. 56,037 analyzed.

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Weiser, 2000 Israel	Cognitive functioning as measured by VMT: Higher for olanzapine and risperidone vs haloperidol: P=0.002 CPT scores: R: 0.541 vs O: 0.516 vs H: 0.300; F=1.003 Calgary Depression Scale: R: 6.73 vs O: 4.53 vs H: 7.75; F=1.974 Rey VLT: R: 38.0 vs O: 40.3 vs H: 36.0; F=0.674 PANSS: R: 66.8 vs O: 63.3 vs 68.2; F=0.568
Wirshing, 2002 United States	NR
Yood, 2009 U.S.A.	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Weiser, 2000 Israel	Haloperidol and risperidone suffered more severe EPS vs olanzapine: P=0.023	
Wirshing, 2002 United States	Increase in glucose levels from baseline: clozapine: +14%; p=.05 olanzapine: +21%; p=.03 haloperidol: +7%; p=.04 Increase/decrease in total cholesterol levels from baseline: risperidone: -6%, p=.04 fluphenazine: -6%; p=.04 13% of olanzapine patients (4) required increases in doses of lipid-lowering agents after beginning treatment	
Yood, 2009 U.S.A.	Olanzapine and clozapine were associated with increased risk of diabetes. Aripiprazole, ziprasidone, risperidone, and quetiapine did not show an increased risk. HR (95% CI) for incident diabetes adjusted for sex, study site, history of AP use, exposure to other pharmacotherapy, overweight, schizophrenia and bipolar disorder code: (Typical antipsychotic = referent) Aripiprazole: 0.93 (0.50, 1.76) Clozapine: 2.58 (0.76, 8.80); p=0.13 (based on 3 events in 147 exposed patients) Olanzapine: 1.71 (1.12, 2.61); p=0.01 (based on 139 events in 17119 exposed patients) Quetiapine: 1.04 (0.67, 1.62) Risperidone: 0.85 (0.54, 1.36) Ziprasidone: 1.05 (0.54, 2.08) Multiple: 1.29 (0.64, 2.62)	The effect estimate for clozapine is imprecise due to the small N's

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Yu, 2008 U.S.A.	Pennsylvania Medicaid claims data.	Retrospective	4 years: 1999-2003
Zhang, 2007, China	Randomly recruited inpatients from Beijing Hui-Long-Guan Hospital, Beijing City, China	Both? (cross-sectional)	NR
Zhao, 2002 United States	IMS Health Lifelink: Integrated Claims Solutions	Retrospective	Average: 181-217 days

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Yu, 2008 U.S.A.	12 months after index prescription.	Olanzapine (N=6929) or quetiapine (n=2321) monotherapy for 30 days or longer, classified based on the initial atypical antipsychotic received during the observation period, regardless of switching pattern. Dose NR.
Zhang, 2007, China	7.5 ± 6.5 years	Mean dose (in chlorpromazine equivalents): 419 ± 337.6 mg/day
Zhao, 2002 United States	NR	risperidone(N=985): 4.02 mg olanzapine(N=348): 10.49 mg

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Yu, 2008 U.S.A.	Adult schizophrenia patients aged 18-64 who were continuously enrolled at least 1 year before and 1 year after the index prescription date, received a do-day monotherapy of either olanzapine or quetiapine after a 90-day washout period during June 2000 to June 2002. Excluded patients who had a managed care organization claim on or after the index prescription date.	Quetiapine (N=2321) vs. olanzapine (6929) // olanzapine cohort (N=2321) matched on propensity score: Mean age: 41.3 vs 42.8 // 41.6 % male: 39.9% vs 52.8% // 40.2% % White: 65.5% vs 55.2% // 64.3% % Black: 28.3% vs 36.7% // 29.1% % Hispanic: 2.0% vs 3.2% // 1.9%	Exposed: 22167 had a pharmacy claim for either drug within index window (2000-2002) Eligible: 9250 met all criteria Selected: all eligible were included	No withdrawals, no loss to followup: subjects selected based on continuous enrollment for 12 months 4642 analyzed.
Zhang, 2007, China	Chronic schizophrenic patients (chronically treated with clozapine, risperidone or typical antipsychotics) and healthy control subjects	Subjects/Controls Mean age (years): 47.3/46.2 % male: 73.4/72% Ethnicity: 100% Han Chinese for both subjects and controls	NR/NR/124patients and 50 controls	Withdrawn: NR Lost to FU: NR Analyzed: 124 schizophrenic patients (clozapine n=57, risperidone n=23, typical antipsychotics n=44) 50 healthy controls
Zhao, 2002 United States	Schizophrenia	Mean age: 48.6 years 53.5% male Ethnicity NR	NR/NR/1333	0/0/1333

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Yu, 2008 U.S.A.	Compared with quetiapine, patients treated with olanzapine had significantly fewer psychiatric hospitalizations, lower pharmacy utilization, and lower medical service costs. Olanzapine (N=2321) vs quetiapine (N=2321): % any psychiatric hospitalization: 28.8% vs 34.0%; p=0.0001 % any emergency visit: 47.0% vs 52.0%: p=0.0007 Any use of clozapine: 4.6% vs 7.1%; p=0.0003 Any use of antidepressants: 65.0% vs 71.3%; p<0.0001 Any use of mood stabilizers: 51.9% vs 57.9%; p<0.0001 Any use of benzodiazepines/hyptnotics/anxiolytics: 47.6% vs 52.1%; p=0.0020 Mean (SD) psychiatric costs, $: 7352 (14,282) vs 9037 (16,904); p=0.0002 Mean (SD) psychiatric hospitalization costs, $: 3149 (10,638) vs 4220 (13,838); p=0.0024 Mean (SD) psychotropic drug costs excluding index drug, $: 1828 (2131) vs 2459 (2477); p<0.0001 Total mean (SD) costs: 16,028 (19,182) vs 17,232 (19,162); p=0.0279 Reduction in costs (postindex minus preindex), adjusted for baseline characteristics: Medical service cost: $2106 vs $869 p=0.0046 Psychiatric cost: $2017 vs $587; p=0.0004 Psychiatirc hospitalization cost: $1566 vs $574; p=0.0043 Drug cost: $3578 vs $3304; p=0.0059 Psychotropic drug cost: $3097 vs $2736; p<0.0001 Total costs: $1473 vs $2435; p=0.0320
Zhang, 2007, China	NA
Zhao, 2002 United States	Average days of treatment: O: 217 vs R: 181; P<.0001

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Yu, 2008 U.S.A.	Use of antiparkinsonian medication during 12-month postindex period was slightly but significantly lower with olanzapine vs quetiapine: 25.9% vs 28.9%; p=0.0214	
Zhang, 2007, China	BMI values: subjects (male/female): 23.9 ± 3.5/25.8 ± 3.6 BMI values: controls (male/female): 21.5 ± 1.9/22.4 ± 2.1 BMI values when matched for BMI on a 1:1 basis: subjects (male/female): 21.5 ± 1.9/22.5 ± 1.9 BMI values when matched for BMI on a 1:1 basis: controls (male/female): 21.2 ± 1.8/22.4 ± 2.0 BMI/BMI gain (kg/m^2)by drug class: Typical: 23.7 ± 3.2/2.5 ± 3.1 Clozapine: 25.4 ± 3.4/3.9 ± 3.2 Risperidone: 22.9 ± 4.1/1.5 ± 3.7	Limited number of female patients
Zhao, 2002 United States	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Zhao, 2002 United States	Database: IMS Health Life Link: Integrated Claims Solutions	Retrospective	October 1, 1996 through December 31, 1998
Uncontrolled studies			
Alvarez, 1997 Spain	Naturalistic: Psychiatry Dept of the Hospital de Sant Pau since 1984 (Spain)	Prospective	6.7 years (mean)
Atkin, 1996 UK/Ireland	Database: Clozaril Patient Monitoring System (CPMS)	Retrospective	1/7/90 to 7/3/94
Buckman, 1999 United States	Database: Illinois Dept of Mental Health and Developmental Disability	Unclear	1990 to 1995

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Zhao, 2002 United States	1 year	Olanzapine= 10.45mg/day Risperidone= 3.32mg/day
Uncontrolled studies		
Alvarez, 1997 Spain	NR	Clozapine 266.9 mg (mean)
Atkin, 1996 UK/Ireland	NR	Clozapine 313 mg
Buckman, 1999 United States	NR	Clozapine

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Zhao, 2002 United States	Schizophrenia	Olanzapine/Risperidone: Mean age (years)=48.9/52.4 % female=44.4/52.2	745/670/670	NR/NR/670
Uncontrolled studies				
Alvarez, 1997 Spain	Treatment resistant Schizophrenia/schizoaffective	Mean age=31.1 62.5% male	NR NR 80	NR NR Unclear
Atkin, 1996 UK/Ireland	Treatment resistant schizophrenia	Mean age=37 66.1% male 89% White 5% African/Afro-Caribbean 3.6% Asian 0.4% Oriental 1.9% Mixed	NR NR 6316	NR NR Year1=6316 Year2=2858 Year3=1625 Year4=661
Buckman, 1999 United States	Treatment resistant schizophrenia	NR NR NR	NR 951 518	NR NR 518

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Zhao, 2002 United States	Duration of treatment: Olanzapine= 213 days Risperidone= 162 days After controlling for patient demographics, patients initiated on olanzapine stayed on therapy 29.4% longer than those initiated on risperidone (P<0.0001) # of patients with >80% of days of receiving medication of interest: Olanzapine= 176 of 423 (41.6%) Risperidone= 64 of 247 (25.9%) Incidence of switching: Patients in olanzapine group were significantly less likely to switch to risperidone than vice versa (OR=0.275, P<0.0001, 95% CI 0.43-0.95) Use of concomitant medications: Olanzapine group significantly less likely to be prescribed an anti-Parkinsonian medication than risperidone group (OR=0.639, P=0.03, 95% CI 0.43-0.95) and had fewer treatment days with such medications (27.4% fewer days, P<0.0001)
Uncontrolled studies	
Alvarez, 1997 Spain	Number of hospitalizations: before=2.65, after=0.35
Atkin, 1996 UK/Ireland	NR
Buckman, 1999 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Zhao, 2002 United States	NR	
Uncontrolled studies		
Alvarez, 1997 Spain	Weight increase (patients): 11 (13%) Seizures (patients): 3 (3%) Serious hematological side-effects: None	Responders vs Nonresponders
Atkin, 1996 UK/Ireland	Agranulocytosis Year1=46/6316(0.7%) Year2=2/2858(0.07%) Year3=0/1625 Year4=0/661 Fatal cases Year1=2/6316 (0.03%) Years2-4=0	
Buckman, 1999 United States	Agranulocytosis Incidence=0.9%	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Bunker, 1996 United States	Clozapine patient monitoring system	Prospective	February 1990 to January 1996
Conley, 1997 United States	Spring Grove Hospital Center	Prospective	1990-1995

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Bunker, 1996 United States	3 years	clozapine for 643 days
Conley, 1997 United States	12 months	clozapine 468 mg/day 12 months

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Bunker, 1996 United States	44.4% paranoid 31.1% undifferentiated 0.02% catatonic 22.2% schizoaffective	Mean age=41.7 years 44.4% male 57.8% Caucasian; 42.2% African American	NR/NR/45	NR/NR/45
Conley, 1997 United States	46.7% schizophrenia 34.7% schizoaffective disorder 10.7% bipolar disorder 8% atypical psychosis	Mean age=35.7 years 60% male Ethnicity: NR	NR/NR/50	NR/NR/50

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Bunker, 1996 United States	NR
Conley, 1997 United States	BPRS total scores: fall 31% from baseline, p<0.0001 BPRS 5 factor scores: fall 32% from baseline, p<0.0001 anergia: fall 24%, p<0.01 anxiety-depression: fall 30%, p<0.0001 activation: fall 31%, p,0.0001 hostility0suspiciousness: fall 46%, p<0.0001 11(33%) patients took longer than 8 weeks to initial respond 16(32%) never achieved clinical response Responders vs non-responders: Age: 33.79 vs 39.88, p<0.05 Years of hospitalization: 2.57 vs 7.2, p<0.05 BRPS Total score: 48.38 vs 44.25, NS Anxiety-depression factor: 9.97 vs 7.5, p<0.05 Anergia factor: 7.29 vs 6.44, NS Thought disturbance factor: 10.71 vs 11.63, NS Activation factor: 6.91 vs 7.44, NS Hostility-suspiciousness factor: 9.35 vs 7.63, p<0.05

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Bunker, 1996 United States	7/25 had emergent DE, average time to onset: 238±179 days, average time to resolution of DE symptoms: 347±190 days baseline vs emergent DE- time to resolution: 261±188 vs 347±190, p<0.05 27 patients had a baseline or emergent DE 15/27(56%) had resolution of DE 10/27(37%) had complete resolution of DE	
Conley, 1997 United States	1 cardiovascular side effect	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
De Hert, 2008, Belgium	Records and patients from University Psychiatric Centre Catholic University Leuven	Retrospective (including a subsample of prospective data for matched group)	NR
Delilliers, 2000 Italy	Database: Italian Clozapine Monitoring System (ICLOS)	Unclear	1995 to 1999
Devinsky, 1991 United States	Chart review	Unclear	1972 to 1988
Dossenbach, 2000 Israel	5 study centers	Prospective	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
De Hert, 2008, Belgium	Historic cohort: 1984-1995 (FGAs) Current cohort: 2000-2005 (SGAs) (At least 1 year treatment exposure; average 3 years treatment exposure)	NR
Delilliers, 2000 Italy	NR	Clozapine 200-350 mg
Devinsky, 1991 United States	NR	Clozapine
Dossenbach, 2000 Israel	18 weeks	olanzapine 5-25 mg/day 18 weeks

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
De Hert, 2008, Belgium	First-episode patients with schizophrenia treated with FGAs matched with first-episode schizophrenia patients treated with SGAs Historic cohort was derived from a cohort of schizophrenic patients admitted between 1973 and 1992	Historic cohort/Current cohort: Age: 22.3±3.2 / 22.1±3.1 Gender (% male): 65.5 / 71.6 Ethnicity: both cohorts were > 95% Caucasian and of native Belgian origin	Historic cohort: 1119 301 148 Current cohort: NR NR 148	NR NR 296 (148 in historic cohort, matched with 148 in current cohort)
Deliliers, 2000 Italy	Treatment resistant schizophrenia	Mean age NR 63% male Race NR	NR NR 2404	NR NR 2404
Devinsky, 1991 United States	Treatment-resistant schizophrenia	NR NR NR	1418 1418 1418	NR NR 1418
Dossenbach, 2000 Israel	chronic schizophrenia	NR	50/NR/48	5/3/48

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
De Hert, 2008, Belgium	N/A
Delilliers, 2000 Italy	NR
Devinsky, 1991 United States	NR
Dossenbach, 2000 Israel	PANSS total score- baseline, mean reduced points, %: 115.3, 17.7, 14.2% BPRS total score- baseline, mean reduced points, %: 44, 9.8, 20.2% (week 6 to week 18 show significant reduced points, p<0.001) Responders- >=20% decrease PANSS: 18(40%) BPRS: 25(55.6%) Responders- 30%, 40% decrease PANSS: 11(24.4%), 2(4.4%) BPRS: 17(37.8%), 13(28.9%) CGI- achieved some degree of improvement: 24(53.3%) Patient Global Impression- improvement: 23(51%)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
De Hert, 2008, Belgium	MetS per antipsychotic in the SGA group (Baseline/Follow-up) (%): Amisulpride: 12.5 / 25 Aripiprazole: 10 / 10 Clozapine: 8.3 / 58.3 Olanzapine: 5.8 / 47.1 Risperidone: 4.1 / 16.7 Quetiapine: 4.8 / 15 Mortality: Historic cohort: 5% died (4.3% suicides, 0.7% cardiovascular) Current cohort: 0% died Historic cohort (data available on 130 patients up-to-date): 6 deaths (5 suicide, 1 cancer) Two deaths while still on an FGA and 6 when treated with an SGA later in the course of illness (4 on clozapine, of which 2 with ketoacidosis; 1 on olanzapine, and 1 on risperidone)	
Deliliers, 2000 Italy	Agranulocytosis 16 cases (0.7%)	
Devinsky, 1991 United States	Seizures # cases=41/1418 (2.9%)	
Dossenbach, 2000 Israel	24(50%) reported >= 1 treatment-emergent adverse event SAS score- baseline vs week 6 vs week 18: 2.7 (vs 1.8 vs 1.6), p<0.001 AIMS score- baseline vs week 6 vs week 18: 2.6 (vs 1.5 vs 1.3), p<0.05 BAS score: NS weight gain: 1.2±4 kg, p=NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Drew, 2002 Australia	Database: Clozaril Patient Monitoring System (CPMS)	Retrospective	5 years
Eberhard, 2006 Sweden	Multicenter	Prospective	NR
Faries, 2008, United States	Post-hoc analysis using data from the risperidone arm of a randomized trial	Retrospective	July 1997 - September 2002
Fleischhaker, 2006, Germany	Four child and adolescent psychiatric departments in four mental heath centers in Germany	Prospective	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Drew, 2002 Australia	NR	Clozapine
Eberhard, 2006 Sweden	5 years	Risperidone
Faries, 2008, United States	Pre-switch (risperidone)/Post-switch (olanzapine) (days) 85.9±77.7 / 241.8±108.3	Pre-switch (risperidone)/Post-switch (olanzapine) (mg/day): Mean maximum = 4.7 / 13.7
Fleischhaker, 2006, Germany	Mean = 7.4 weeks	Clozapine/Olanzapine/Risperidone Mean dose (mg): 321.9±156.5/16.6±7.1/3.9±1.7 Dose range (mg): 125.0-600.0/7.5-30.0/1.0-6.0

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Drew, 2002 Australia	Schizophrenia/schizoaffective	NR NR NR	NR 42 32	NR NR 32
Eberhard, 2006 Sweden	Individuals treated with risperidone for at least 2 weeks	Mean age (years): 38.5	NR/223/223	NR/57/166
Faries, 2008, United States	Diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform disorder, greater than 18 years of age, and randomized to risperidone therapy and either switched or did not switch to olanzapine therapy	**Switchers/Non-switchers** Mean Age ± SD (years): 43±13.1/42.2±11.5 Gender (% female): 60.5/34.2 Ethnicity (%): Caucasian: 55.8/54.4 African American: 30.2/34.8 Other: 14.0/10.8	NR 221 218	NR NR 201
Fleischhaker, 2006, Germany	Adolescent inpatients (n=51) who started treatment with clozapine (n=16), olanzapine (n=16), and risperidone (n=19) in open clinical trials 31 adolescents had a diagnosis of schizophrenia	Clozapine/Olanzapine/Risperidone Mean age (y±SD): 17.2±1.8/15.8±1.4/15.6±2.6 Gender (n male): 11/9/13 Ethnicity: NR	NR NR 51	NR NR 51

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Drew, 2002 Australia	NR
Eberhard, 2006 Sweden	Subjects diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder had significantly higher SUM-TD scores than those with other diagnoses (P<0.001). 5 patients had TD at study endpoint, while the 12 patients who had TD at study entry had recovered at endpoint. All analyses of AIMS ratings were non-significant
Faries, 2008, United States	NA
Fleischhaker, 2006, Germany	NA

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Drew, 2002 Australia	Agranulocytosis: # cases=1/32 (3.1%) Hospitalization(% pts admitted ≥ 1 day) Pre-clozapine 2nd year=56.3% 1st year=59.4% Post-clozapine Year1=81.3% Year2=31.3% Year3=21.9% Year4=18.8% Year5=18.8%	Clozapine-naïve; commenced Clozapine in Australian Capital Territory (ACT) before 7/1/94
Eberhard, 2006 Sweden	NR	Multiple analyses with subgroups and subcomparisions by diagnosis. I had a hard time piecing out the different results and what groups were being compared.
Faries, 2008, United States	**Switchers/Non-switchers:** Weight (mean±SD, in Kg): Baseline=87.8±20.2 / 87.6±21.5 Endpoint=90.7±22.8 / 90.1±21.9 Change=1.4±3.7 / 0.4±3.9	Small size and no comparative group
Fleischhaker, 2006, Germany	Clozapine/Olanzapine/Risperidone Tardive dyskinesia (n,(%)): 0(0)/0(0)/0(0) Weight gain (n,(%)): 9(56.3)/11(68.8)/7(36.8); p=0.16 Mean weight gain after 6 weeks (kg): 2.5/4.6/2.8	Comedication

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Hagg, 1998 Sweden	Single site Naturalistic: Gallivare Hospital	Cross-sectional, prevalence study	Years treated mean (range): clozapine 3 (0.1-6) typical APs 6 (0.2-22)
Henderson, 2000 United States	Chart review: outpatient clinic of urban mental health center	Retrospective	5 years
Henderson, 2005 United States	Autopsy reports, medical records	Retrospective	January 1992 to December 2003
Herrman et al, 2004 Canada	Database: administrative health care databases in Ontario, Canada	Retrospective	April 1, 1997 through March 31, 2002

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Hagg, 1998 Sweden	No follow-up (snapshot)	Clozapine Typical APs Mean dose NR
Henderson, 2000 United States	NR	Clozapine
Henderson, 2005 United States	90 months	Clozapine; dose NR
Herrman et al, 2004 Canada	NR	Risperidone Olanzapine Typical antipsychotics

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Hagg, 1998 Sweden	Patients treated with clozapine or typical APs at the time study was conducted. 85% schizophrenia 4.6% paranoid psychosis 3% cycloid psychosis 3% affective/schizo-affective psychosis	Mean age: clozapine 41, typical APs 48 59% male Ethnicity NR	214/142/130 Clozapine n=63 Typical APs n=67	NR NR 130 analyzed
Henderson, 2000 United States	Schizophrenia Schizoaffective disorder	Mean age=36.35 73.2% male 91.5% white	NR 101 82	NR NR 82
Henderson, 2005 United States	Schizophrenia Schizoaffective disorder	Mean age=36.5 years 72% male 89% white	NR NR 96	N/A N/A 96
Herrman et al, 2004 Canada	Patients over age 65 who were given at least 2 successive prescriptions and received enough drug for at least 30 days of observation.	Mean age approximately 82 years (SD 7.5) 69% female Ethnicity not reported	NR NR 11,400	NR NR 11,400

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Hagg, 1998 Sweden	NR
Henderson, 2000 United States	NR
Henderson, 2005 United States	NR
Herrman et al, 2004 Canada	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Hagg, 1998 Sweden	Clozapine vs typical APs, Prevalence: Hyperglycemia 33 vs 19% (p=0.07) Type 2 diabetes 12 vs 6% (ns) Impaired glucose tolerance (IGT) 10 vs 3% (ns) Type 2 DM or IGT 22 vs 10% (p=0.06) Women with type 2 diabetes or IGT, clozapine vs typical APs: 9/27 (33.3%) vs 2/26 (7.7%) (p=0.04) Body mass index, all subjects: 27 vs 28 kg/m2 (ns) Body mass index, subjects with diabetes mellitus or IGT: 27 vs 30 kg/m2 (ns)	12 (19%) clozapine subjects had concomitant treatment with typical APs, most often haloperidol (n=6). Body mass index was similar between clozapine patients with and without diabetes/IGT. Clozapine patients tended to be younger and treated for fewer years than patients on typical APs.
Henderson, 2000 United States	Diagnosis of Type II Diabetes=30/82 (36.6%) Weight gain: linear coefficient of 1.16 lb/month (SE=0.18) (mixed-effects model, t-6.62, df-80, p=0.0001)	
Henderson, 2005 United States	Kaplan-Meier estimates for overall 10-year: Mortality=9% New-onset diabetes=34%	
Herrman et al, 2004 Canada	Hospital admission for stroke: typical antipsychotic users: N=10 risperidone users: N=58 olanzapine users: N=24 Crude stroke rate per 1.000 person years: typical antipsychotic users: 5.7 risperidone users: N=7.8 olanzapine users: N=5.7 (NS) RR relative to typical antipsychotic use: olanzapine: 1.1 (95% CI 0.5, 2.3) risperidone: 1.4 (95% CI 0.7, 2.8) RR of risperidone relative to olanzapine: 1.3 (95% CI 0.8, 2.2)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Hofer, 2003 Austria	inpatients unit of the Department of Psychiatry of Innsbruck University Clinics	Prospective	1989-1996
Honigfeld, 1996 United States	Database: Clozapine National Registry System	Unclear	2/1990 to 12/1994
Kane, 1994 United States	the inpatients service at Hillside Hospital	Prospective	NR
Killian, 1999 Australia	Adverse Drug Reactions Advisory Committee (ADRAC) of Australia	Unclear	Jan. 1993 to March 1999

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Hofer, 2003 Austria	8 weeks	Clozapine 263.5 mg/day for at least 8 weeks
Honigfeld, 1996 United States	NR	Clozapine
Kane, 1994 United States	52 weeks	Clozapine 599 mg/day 52 weeks
Killian, 1999 Australia	NR	Clozapine range: 100-725 mg/d myocarditis pts took cloz. a median of 15d (range: 3 22d) before myocarditis developed Cardiomyopathy pts took cloz. a median of 12 months (range: 2-36 m) before cardiomyopathy developed

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Hofer, 2003 Austria	Schizophrenia or schizophreniform disorder	Mean age=28.7 years 75.5% male Ethnicity: NR	NR/NR/95	NR/NR/95
Honigfeld, 1996 United States	Treatment resistant schizophrenia	NR NR NR	NR NR 99,502	NR NR 99,502
Kane, 1994 United States	Schizophrenia or schizoaffective disorder	Mean age=27.6 years 66% male 84% white; 14% black; 2% other	NR/NR/56	NR/NR/34
Killian, 1999 Australia	Clozapine-using patients (article did not specify diagnosis of pts in registry)	Mean age: 36y 87% male Ethnicity: NR	8000/ 43/ 33	NR/ NR/ 33

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Hofer, 2003 Austria	Multiple linear regression: only age found to be a significant predictor of CGI (F=4.22, p=0.045)
Honigfeld, 1996 United States	NR
Kane, 1994 United States	Correlations of Simpson-Angus Akinesia item with BPRS anergia factor: r, p value baseline (n=56): 0.68, p=0.00 week 3 (n=49): 0.59, p=0.00 week 6 (n=47): 0.43, p=0.00 week 12 (n=27): 0.48, p=0.01 week 26 (n=28): 0.40, p=0.03 week 39 (n=24): 0.37, p=0.07
Killian, 1999 Australia	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Hofer, 2003 Austria	1 seizures 1 increased liver enzyme level Frequently reported side effects: week 1-3(%) vs week 4-6(%) First episode (n=39) concentration difficulty: 51.3 vs 13 asthenia: 48.7 vs 26.1 sedation: 20.5 vs 0 failing memory: 25.6 vs 0 increased duration of sleep: 41.3 vs 30.4 increased salivation: 28.2 vs 17.4 diminished sexual desire: 41.0 vs 13.0 Multiple episode (n=556) concentration difficulty: 55.3 vs 31.5 asthenia: 53.6 vs 25.8 sedation: 35.7 vs 20.0 failing memory: 28.6 vs 17.1 increased duration of sleep: 39.3 vs 25.7 increased salivation: 23.2 vs 8.6 diminished sexual desire: 35.8 vs 25.7	
Honigfeld, 1996 United States	Agranulocytosis Cases=382(0.38%) Fatal cases=12(0.012%)	
Kane, 1994 United States	NR	
Killian, 1999 Australia	Cardiomyopathy: 8 cases (of 8000 clozapine pts; 0.10%) Myocarditis: 15 cases (of 8000 clozapine pts; 0.19%) (10 additional cases were not supported by objective clinical or investigational findings) Deaths: 33.3% (5 of 15) myocarditis pts and 12.5% (1 of 8) cardiomyopathy pts died	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Kim, 2008, South Korea	Department of Psychiatry, Bundang CHA General Hospital, South Korea	Prospective	December 2004 - July 2007
Koller, 2001 United States	MedWatch Drug Surveillance System	Retrospective	January 1990 to February 2001

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Kim, 2008, South Korea	NR	85.9±77.7 / 241.8±108.3
Koller, 2001 United States	NR	Clozapine 362 mg

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Kim, 2008, South Korea	Patients with first-episode schizophrenia or schizoaffective disorder, between 17 and 60 years of age, with an IQ above 80, and receiving treatment of long-acting injectable or oral risperidone as outpatients	RLAI/Oral Age (years): 32.5±10.6/31.0±10.1 Gender (%male): 32/40 Ethnicity: NR	NR 55 (25 assigned to risperidone long-acting injection (RLAI) group, 30 assigned to oral risperidone group)/ 50 (22 assigned to RLAI group, 28 assigned to oral risperidone group)	NR NR 50
Koller, 2001 United States	clozapine-associated diabetes or hyperglycemia	Mean age=40 years Gender: NR Ethnicity: NR	NR/NR/384	NA/NA/384

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Kim, 2008, South Korea	1-year medication compliance (%mean±SD): RLAI = 85.7±21.4 Oral risperidone = 54.3±32.8 2-year medication compliance (%mean±SD): RLAI = 81.4±26.6 Oral risperidone = 54.6±32.1 Non- or partial adherence (%): RLAI = 32% Oral risperidone = 68% Good adherence (%): RLAI = 68% Oral risperidone = 32% 1-year relapse (%): RLAI = 18% Oral risperidone = 50% 2-year relapse (%): RLAI = 23% Oral risperidone = 75%
Koller, 2001 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Kim, 2008, South Korea	Tardive dyskinesia was observed in one patient in the RLAI group	Sample size was small
Koller, 2001 United States	clozapine was discontinued in 110 cases (54 cases follow-up were available) 42 improved in metabolic status 11 had no change in metabolic status 26 no longer required hypoglycemic drug therapy 18 glucose levels returned to normal 80 patients had metabolic acidosis or ketosis accompanied the hyperglycemia 73 with new-onset diabetes (blood glucose level >= 500 mg/dL) 51 with new-onset diabetes (blood glucose level >= 700 mg/dL) 32 with new-onset diabetes occurred within 3 months of the initiation of clozapine therapy (blood glucose level >= 700 mg/dL) 26 had acidosis or ketosis 25 died during hyperglycemic episodes 16 had acidosis or ketosis 146 patients had body weight data 38 had no clear evidence of obesity or substantial weight gain	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Kopala, 2005 Canada	Nova Scotia Early Psychosis Program in Halifax	Prospective open-label dose ranging study	NA
Kozma, 2004 (poster) United States	Database: Medstat's Medicaid database	Retrospective	1999-2002
Lasser, 2004 Europe and Canada	Europe and Canada multicenter trial	Prospective	12 months

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Kopala, 2005 Canada	2 years	Starting dose of quetiapine was 25 mg and then the dose was titrated up to a maximum of 800 mg/day depending on symptom response and tolerability.
Kozma, 2004 (poster) United States	NR	Atypical antipsychotics overall Olanzapine Risperidone Quetiapine Haloperidol Benzodiazepines
Lasser, 2004 Europe and Canada	239 days	Risperidone 25mg, 50mg

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Kopala, 2005 Canada	Inpatients (n = 10) and outpatients (n = 29), ages of 17 and 42 who met DSM IV criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder. Subjects with > 6 months of cumulative exposure to antipsychotic medications or had been psychotic > 2 years were excluded.	Mean age 23.2 years 82.1 % male 100% Caucasian	NA	19/19/20
Kozma, 2004 (poster) United States	Age 60 or older, evidence of dementia treatment (2 or more claims containing a primary or secondary diagnosis of dementia), initial use (I.e., following a 6-month or longer period of no use) of 1 of 3 classes of drugs: atypical antipsychotics (risperidone, olanzapine, or quetiapine), haloperidol, or benzodiazepines.	Median age 78-82 among groups; Among patients taking atypical antipsychotics, 56% were Caucasian, 17% African American; among patients taking conventional antipsychotics, 45% were Caucasian and 21% African American.	NR NR 26,456	NR NR 26,456
Lasser, 2004 Europe and Canada	Schizophrenia or schizoaffective disorder	Mean age: 70.9 years 53% male 100% white	725/57/57	NR/1/57

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Kopala, 2005 Canada	See safety outcomes
Kozma, 2004 (poster) United States	NR
Lasser, 2004 Europe and Canada	baseline vs change at endpoint, p vs baseline PANSS total: 73±2.1 vs -10.5±1.5, p<0.001 Positive symptoms: 20.6±0.8 vs -3.2±0.6, p<0.001 Negative symptoms: 19.7±0.8 vs -2.8±0.5, p<0.001 Disorganized thoughts: 17.7±0.7 vs -2.0±0.4, p<0.001 Anxiety/depression: 8.2±0.5 vs -1.6±0.4, p<0.001 Hostility/excitement: 6.8±0.4 vs -0.9±0.3, p<0.01 baseline vs endpoint CGI- not ill or with very mild or mild illness: 28% vs 69% CGI- marked or severe illness: 14% vs 0% CGI- at least 1 point improvement in CGI severity scores: 55%

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Kopala, 2005 Canada	BMI and weight at baseline and 24 months grouped by BMI less than 25 Base BMI 21.5 weight 67.0 kg 2 yrs BMI 25.6 weight 79.1 kg BMI baseline vs. 2 years P < 0.001 BMI 25 or greater Base BMI 29.1 weight 84.3 kg 2 yrs BMI 30.3 weight 86.7 kg BMI baseline vs. 2 years P < 0.001	
Kozma, 2004 (poster) United States	Stroke-related event (defined as an acute inpatient hospital admission for a stroke-related event within 90 days following initiation of treatment with the index medication): Unadjusted rates were not statistically significant, reporting is unclear: states rates were: 0.87%, 0.97%, 0.88%, 0.58%, 1.19%, 1.11% 1.04% for atypical antipsychotics overall, olanzapine, risperidone, quetiapine, haloperidol, and benzodiazepine groups, respectively.	
Lasser, 2004 Europe and Canada	42(74%) reported adverse events insomnia: 14% constipation: 12% bronchitis: 12% psychosis: 11% rhinitis: 11% 1 died with a myocardial infarction baseline vs mean change at endpoint, p vs baseline ESRS total: 10.2±1.5 vs -3.1±0.8, p<0.001 Patient questionnaire: 4.0±0.7 vs -1.4±0.5, p<0.01 Parkinsonism total: 10.6±1.5 vs -3.6±0.9, p<0.001 Parkinsonism severity: 1.7±0.2 vs -0.4±0.2, p<0.05 Dyskinesia total: 2.7±0.7 vs -0.6±0.3, NS	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Lasser, 2004 United States	NR	Prospective	NR
Lieberman, 1992 Alvir 1993 United States	Database: Caremark Patient Monitoring System (CPMS) from 2/5/90 to 4/30/91	Unclear	>/= 3 weeks
Lindstrom, 1989 Sweden	Hospital records and interviews	Retrospective	July 1, 1974 to December 31, 1986

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Lasser, 2004 United States	8 weeks	Olanzapine or risperidone for 8 weeks
Lieberman, 1992 Alvir 1993 United States	NR	Clozapine mean maximum dose=451.9 mg
Lindstrom, 1989 Sweden	NR	Clozapine

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Lasser, 2004 United States	Schizophrenia or schizoaffective disorders	Mean age=49.9 years 60.8% male 63.6% white	NR/NR/552	NR/NR/375
Lieberman, 1992 Alvir 1993 United States	Schizophrenia	Mean age NR 62% male Race NR	17,042 11,555 11,555	NR NR 11,555
Lindstrom, 1989 Sweden	Schizophrenia or schizoaffective disorders	Mean age (years): 36.1 66% males	NR/NR/99	2/3/96

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Lasser, 2004 United States	NR
Lieberman, 1992 Alvir 1993 United States	NR
Lindstrom, 1989 Sweden	More than one third of participants significantly improved while on clozapine, while another one third moderately improved. 35 patients discontinued treatment of clozapine during the study period, 8 of those showed significant improvement before stopping the medication At the initiation of clozapine 3 patients were employed, however 2 yeas later, of those still on clozapine, 24 were employed.

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Lasser, 2004 United States	patients with >= 7% weight increase olanzapine adult smokers: 25/82(30.5%) olanzapine adult nonsmokers: 16/55(29.1%) olanzapine elderly smokers: 4/27(14.8%) olanzapine elderly nonsmokers: 4/35(11.4%) risperidone adult smokers: 11/82(13.4%) risperidone adult nonsmokers: 7/43(16.3%) risperidone elderly smokers: 0/20(0%) risperidone elderly nonsmokers: 3/31(9.7%) Pearson's correlation analysis between smoking and weight: risperidone-treated patients: r = -0.037 olanzapine-treated patients: r = 0.029	
Lieberman, 1992 Alvir 1993 United States	Agranulocytosis # cases/fatal cases=73/2 Cumulative incidence (year1/year1.5): 0.8%/0.91%	
Lindstrom, 1989 Sweden	2 patients withdrew from the study due to leukopenia or agranulocytosis, neither were fatal outcomes. Common, but usually mild side effects included: sedation, hypersalivation, weight gain, and obstipation. 4 patients experienced grand mal seizures while on clozapine, however these were controlled with other medications. 4 patients died while on clozapine, however there was no direct correlation found between the deaths and the use of clozapine, 2 of these deaths were suicides.	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Lindstrom, 2007, Sweden	Patients enrolled in a national, multicenter, point-prevalence, 5-year longitudinal Phase IV trial	Prospective	1995-2000
Lund, 2001 United States	Database: Iowa Medicaid program claims/prescription database	Unclear	1990 to 1994
Maskasame, 2007, Thailand	Medical record review: Srinagarind Hospital, Khon Kaen, Thailand	Retrospective	NR
Mladsi, 2004 United States	Three acute care inpatient mental health facilities	Retrospective	May 1, 1998 and June 30, 2000

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Lindstrom, 2007, Sweden	Variable	NR
Lund, 2001 United States	Clozapine=25.5 months Typical APs =24.5 months	Clozapine Typical Antipsychotics
Maskasame, 2007, Thailand	2 years	Doses were recorded but no mean dose was reported. Patient who developed neutropenia received 25mg/day of clozapine
Mladsi, 2004 United States	Length of stay- less than 30 days	Risperidone 4.45 mg Olanzapine 14.04 mg Quetiapine 350.33 mg

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Lindstrom, 2007, Sweden	Patients with schizophrenia or a related disorder according to DSM-IV and treated with risperidone as the main antipsychotic drug for at least 1 month. During the following 5 years, some patients were switched to other antipsychotic compounds or were drug-free Males and females >18y; in- and out-patients; responders or partial responders to antipsychotic drugs	Background variables of all included patients (n=225) Age (y): 38.5±11.7 (range 18-79) Gender (n male): 132 Ethnicity: NR	Exposed:225 Eliglble:225 Selected:101	Withdrawn: NR Lost to FU: NR Analyzed: 101
Lund, 2001 United States	Schizophrenia	Mean age=41.9 59.2% male Race NR	NR 4770 3013	NR NR 3013 (clozapine=552, CAPD=2461)
Maskasame, 2007, Thailand	Schizophrenic out-patients who received clozapine from January 1, 2003-December 31, 2005	Mean Age: 32 years; % Male: 58.5%, Ethnicity: NR	NR/117/65	0/0/65
Mladsi, 2004 United States	Schizophrenia 59% Schizoaffective 41%	Mean age 40 years 62% male 52% white 39% black 9% other	NR NR 327	NA NA 327

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Lindstrom, 2007, Sweden	
Lund, 2001 United States	NR
Maskasame, 2007, Thailand	NR
Mladsi, 2004 United States	Mean length of stay was 12.4 days (SD 6.5) for risperidone patients, 11.3 days (SD 5.7) for olanzapine patients, and 13.7 days (SD 6.5) for quetiapine GAF scores at discharge (45.9 [SD 10.3] for risperidone, 46.2 [SD 10.1] for olanzapine, and 44.3 [12.2] for quetiapine)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Lindstrom, 2007, Sweden	Frequency of Parkinsonism/dystonia according to the ESRS instrument over 5 years (Score 0-1 / Score 2-4 / Score 5-6 / n): 495/574 / 240/158 / 10/13 / 745 Abnormal involuntary movements: 23 of 166 patients (14%) had TD Social Outcomes: Mean number of days in hospital decreased from 41 to 10 days Mean number of days in sheltered accommodations increased from 28 to 63 Net decrease in the number of patients who lived independently from 83% to 71% One patient (of 101) had 365 hospital days during year 5, and 9 others had any hospital days (range 3-138) 15-26% of patients had no social contacts (except with health service staff) 29-37% reported meeting friends or peers <1 time per week 12% of patients worked or studied full-time 14% worked or studied half-time 75% were on sick leave or had disability pension Mortality: 8 patients died during the 5 year trial	
Lund, 2001 United States	Diabetes Total cohort 21 (4%) vs 78 (3.4%); p=0.62 Patients aged 20-34 11/222 (5%) vs 15/768 (2%) RR 2.5, 95% CI 1.2 to 5.4	Age
Maskasame, 2007, Thailand	Neutropenia was found in one patient (incidence rate = 1.5%, incidence density = 0.01/year). No leukopenia or agranulocytosis were found.	WBC was not checked before starting clozapine in patient who developed neutropenia
Mladsi, 2004 United States	NR	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Munro 1999 UK and Ireland	Clozapine drug registry review	Retrospective	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Munro 1999 UK and Ireland	January 1990 - April 1997	Mean clozapine dose after 12 w treatment: 388 mg/day (95% CI 384-391) Mean maximum clozapine dose: 462 mg/day (95% CI 458-466) 41% of subjects had a peak dose >500 mg/day; 5% of subjects exceeded the recommended maximum dose of 900 mg/day

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Munro 1999 UK and Ireland	Treatment-resistant schizophrenic patients prescribed clozapine	Mean age (at 1st blood test): males: 35.4 y (range 9.6-84.1); females: 39.7 y (range 13.8-90.4) Male: 67 % Ethnicity: 89% Caucasian; 5% African-Caribbean origin; 4% Asian; 2% mixed race; <1% Oriental	NR NR 12760	Withdrawn: 283 Caucasian and 33 African-Caribbean subjects withdrew due to neutropenia All other withdraws NR Lost to FU: NR Analyzed: 12760

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Munro 1999 UK and Ireland	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Munro 1999 UK and Ireland	Agranulocytosis: Cumulative incidence: 0.73% Peak risk occurred at 6-18 weeks with an incidence of 0.7% Mortality rate: 0.016% For each 10 year increase in age on starting clozapine, the hazard of developing agranulocytosis increased by 53% (P=0.0001, hazard ratio 1.528, 95% CI 1.315-1.777) Compared with Caucasians, Asian subjects had 2.4 times the risk of developing agranulocytosis (P=0.03, hazard ratio 2.388, 95% CI 1.098-5.194) The risk in Oriental/Mixed-race and African-Caribbean subjects was nonsignificant (P=0.84, P=0.61, respectively) For each 100mg increase in the maximum dose the risk of agranulocytosis decreased by 21% (P= 0.0001; hazard ratio 0.787, 95% CI 0.702-0.882) <u>Neutropenia:</u> Cumulative incidence: 2.7% Peak risk occurred at 6-18 weeks with an incidence of 1.27% For each 10 year increase in age on starting clozapine, the hazard of developing neutropenia decreased by 17% (P=0.0003, hazard ratio 0.834, 95% CI 0.756-0.919) The hazard ratio for African-Caribbean subjects was 1.77 (95% CI 1.208-2.583, P=0.0033) There was no significant difference in Oriental/Mixed-race or Asian subjects (P=0.25 and P=0.497, respectively) For each 100mg increase in the maximum dose the risk of neutropenia decreased by 31% (P= 0.0001; hazard ratio 0.688, 95% CI 0.647-0.731) <u>Monitoring Interval:</u> Four-weekly/Two-weekly # subjects treated: 5199/1510 # of hematological fatalities: 0/0 # (%) of neutropenia cases: 13 (0.25)/71 (4.7%) # (%) of agranulocytosis cases: 2 (0.04)/4 (0.26)	Incomplete tables, poor data presentation

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Perez, 2008, Spain	77 acute hospital units in Spain	Prospective	March 2002 - October 2004
Rastogi, 2000 UK	NR	Prospective	NR
Reid, 1998 United States	Database: Texas MH System	Unclear	1991 to 1996
Still, 1996 United States	a 400-bed state psychiatric hospital	Prospective	April to August 1994

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Perez, 2008, Spain	Acute: admission to discharge, and Long-term: discharge to 12 months	Mean doses at discharge: quetiapine = 719.6 mg/day risperidone = 8.0 mg/day Mean doses at 12 months: quetiapine = 718.5 mg/day risperidone = 7.0 mg/day
Rastogi, 2000 UK	6 months	clozapine 150-300 mg 6 months
Reid, 1998 United States	NR	Clozapine
Still, 1996 United States	12 weeks	Risperidone titrated a week to 3mg twice daily. The mean dosage for the five subjects who completed 12 weeks treatment is 7.6 mg at week 9 and 8 mg at week 12.

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Perez, 2008, Spain	Patients admitted to an acute unit with schizophrenia, schizophreniform or schizoaffective disorder who were prescribed quetiapine or risperidone within the first week of treatment	**Quetiapine/Risperidone:** Mean age: 37.2/36.4 Gender (% male): 63.6/67.8 Ethnicity: NR	NR 492 Selected: Intent to Treat population: 466 (quetiapine=345, risperidone=121) Per protocol population: 422 (quetiapine=311, risperidone=111) Safety population: 470	**Quetiapine/Risperidone:** Withdrawn: NR Lost to FU: time of discharge: 43/9 6-month follow-up: 89/28 12-month follow-up: 31/13 Analyzed: baseline: 345/121 time of discharge:
Rastogi, 2000 UK	Schizophrenia	Mean age=37.8 years 71% male Ethnicity: NR	NR/NR/31	NR/NR/31
Reid, 1998 United States	Schizophrenia/ Schizoaffective	NR NR NR	NR NR NR	NR NR NR
Still, 1996 United States	Schizophrenia or schizoaffective disorder	Mean age=41.2 years 60% male Ethnicity: NR	NR/NR/10	5/0/5

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Perez, 2008, Spain	
Rastogi, 2000 UK	Global impression: 21(67.7%) patients were rated as improved by clinicians 18(58.1%) patients self-rated as improved Six monthly outcome measure for the basic everyday living skills scale: Mean % improvement self-care: 15% domestic skills: 20% community skills: 17% activity and social skills: 22%
Reid, 1998 United States	NR
Still, 1996 United States	No subjects improved after being switched to risperidone PANSS, LPCF increased from baseline, but no significant changes: patients who were switched from clozapine tended to worsen when taking risperidone (data NR) The mean total scores on the PANSS, the PANSS positive symptom subscale and the BPRS met the study's 20% criterion for a clinically significant change at week 6 through week 12 (data NR) CGI scores: 2 no change; 3 minimally worse; 4 much worse; 1 very much worse

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Perez, 2008, Spain		
Rastogi, 2000 UK	NR	
Reid, 1998 United States	Suicide 1 case Annual rate=12.74 per 1000,000	
Still, 1996 United States	3 decreased concentration 3 impaired memory 4 irritability 3 akathisia, confusion Akathisia scale showed significant different worsening of symptoms	Patients switched from clozapine to risperidone

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Tadger, 2008, Israel	Inpatients and their files from inpatient rehabilitation and day care units	Prospective (some data was collected retrospectively, however)	NR
Taylor, 2009, UK	Pharmacy computer records	Retrospective	Clozapine group: March 2002-October 2006 Risperidone group: August 2002-October 2004

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Tadger, 2008, Israel	One year or longer for patients treated with second-generation antipsychotic agents; NR for patients treated with first-generation antipsychotics	NR
Taylor, 2009, UK	Clozapine/Risperidone Mean duration of treatment (months) (mean±SD): 12.3±18.6/5.9±8.7	Clozapine/Risperidone: Mean dose at cessation (mg/day) (mean±SD): 360±159/34.5±12.2

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Tadger, 2008, Israel	Inpatients treated with second-generation antipsychotics for 1+ year (n=70), and inpatients treated with first-generation antipsychotics (n=30). 91% of subjects were diagnosed with schizophrenia, 9% were diagnosed with other psychiatric disorders.	Mean age: 47.4±12.4 years Gender: 60% male Ethnicity: NR	NR NR 100 (risperidone N=40, olanzapine N=30, typical N=30)	NR NR NR
Taylor, 2009, UK	161 Clozapine discontinuers matched with 161 Risperidone discontinuers	Clozapine/Risperidone Age at discontinuation (mean±SD) (y): 40.0±12.6/39.9±13.1 Gender (n male): 99/99 Ethnicity (n): White: 72/61 Black (African/Caribbean): 61/79 Asian: 13/9 Mixed 15/12	Clozapine/Risperidone Exposed: 592/277 Eligible: 224/250 Selected: 161/161	Clozapine/Risperidone Withdrawn: NR/NR Lost to FU: NR/27 Analyzed: 161/161

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Tadger, 2008, Israel	N/A
Taylor, 2009, UK	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Tadger, 2008, Israel	**Increase/decrease in BMI (%):** -1.00 (lost weight): typical=23.3 risperidone=17.9 olanzapine=6.9 0.00 (maintained weight): typical=50.0 risperidone=59.0 olanzapine=48.3 1.00 (gained weight): typical=26.7 risperidone=17.9 olanzapine=37.9 2.00 (gained weight): typical=N/A risperidone=5.1 olanzapine=3.4 3.00 (gained weight): typical=N/A risperidone=N/A olanzapine=3.4	
Taylor, 2009, UK	Death as a reason for discontinuation (n, (%)): Clozapine/Risperidone/OR (95% CI)/McNemar's x2, df=1 21 (13.0)/3 (1.9)/7 (2.09-23.5)/13.5 (p=0.0003) Clozapine/Risperidone: Mortality rate: 8.5 (95%CI 5.53-13.07) per 1000 patient years/5.3 (95% CI 1.7-16.61) per 1000 patient years	Funder: Janssen-Cilag, Novartis, IVAX

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame
Umbricht, 1994 United States	Chart review	Retrospective	12 months
Wilson, 1993 United States Second paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first year	Chart review of first 100 pts starting clozapine treatment (Dammasch State Hospital; Wilsonville, Oregon)	Unclear	May 1990 to December 1991

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Exposure period	Interventions mean dose
Umbricht, 1994 United States		Clozapine
Wilson, 1993 United States Second paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first year	1 year follow-up (as well as review of 6 months prior to start of clozapine treatment); at 1 year follow up 37 pts had been discharged to community and 63 pts remained hospitalized	Clozapine begun at 25 mg/d and titrated upwards; Mean clozapine dose for pts at 3 months was 463 mg/d; Mean dose for pts who remained hospitalized and continued clozapine 564 mg/d

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Umbricht, 1994 United States	Schizophrenia	Mean age=28.7 68% male 85.4% white	NR NR 82	NR NR 68
Wilson, 1993 United States Second paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first year	Schizophrenia: 67%; Schizoaffective disorder: 26%; Bipolar with psychotic features: 6%; Organic delusional disorder: 1% 12% had previous history of seizures - 8% idiopathic and 4% followed head trauma	Mean age: 37y Range: 20-61y 55% male 94% white	NR/ NR/ 100	9 NR 100 1 pts dropped out after leukopenia and 1 pts dropped out after seizure

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Umbricht, 1994 United States	NR
Wilson, 1993 United States Second paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first year	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes	Comments
Umbricht, 1994 United States	60% with ≥ 10% weight gain	72% neuroleptic-treatment resistant
Wilson, 1993 United States Second paper in a series studying clozapine-treated pts in Dammasch State Hospital; this study analyzed the pts entered into the cohort in the first year	Seizures: 10% of pts (5 men and 5 women) had at least 1 seizure; they occurred at a mean dose of 323 mg/d Of the 10 pts with seizures: 6 pts were smokers, 4 were nonsmokers 4 pts of 12 with previous history had seizures; 6 of 88 pts without this history had seizures 1 of 9 pts with previous head trauma had seizure	1 pt reported to have died of pneumonia (not related to drug) 4 mos after discontinuing clozapine

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Advokat, 2004	No, excluded patients with incomplete data	No withdrawals reported	Yes	Yes	No, ratings probably unblinded because performed by psychologists/ psychiatrists on staff at hospital
Advokat, 2004	Yes for overall group; but unclear for subset for which length of stay was determined, which was only those who were discharged during study period and N was NR	Unclear; implied that length of stay not available for all patients, but N=NR	Yes for some, no for length of stay.	No	Unclear
Agelink, 2001	Method NR, unable to determine.	Yes (9%)	Yes	Yes	Yes
Akkaya, 2007	Yes	N/A: retrospective analysis excluded 32.7% of pts with an initial admission and dx but no follow-up visit	Yes	Yes	Possible missing data inherent in chart review - AEs not gathered uniformly - but direction of potential bias is unknown.
Alvarez, 1997 Spain	No: AE withdrawals during first 3 weeks not included	NR	Yes	Yes	Yes
Al-Zakwani, 2003	No, excluded patients who had a behavioral health benefit carve-out and those who were not continuously enrolled for 18 months	No withdrawals reported.	Yes	Yes	NR

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Advokat, 2004	No and only baseline demographic data reported; unclear if differences in prognostic factors	Yes	Poor	
Advokat, 2004	No and there were differences between groups in rates of patents taking concomitant typical AP's : olanzapine= 57%, risperidone=38%, quetiapine = 64%, and clozapine = 14%	No; ≥ 3 months	Poor	
Agelink, 2001	Yes	Yes	Fair	
Akkaya, 2007	Yes; bivariate comparisons	N/A	Fair	
Alvarez, 1997 Spain	NR	Yes	Fair	
Al-Zakwani, 2003	Yes	Yes	Fair	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Ascher-Svanum, 2004 US-SCAP Study Interim Results	Not entirely clear. Broad range of patients enrolled, with few exclusion criteria but method of obtaining participants not described well enough to determine. Also, for this sub-study, patients discontinuing treatment prior to 1 year were excluded.	None	Yes	Yes	No. Data extracted from medical records. Methods not described (e.g. blinding, validation).
Ascher-Svanum, 2008	Yes	Yes	Yes	Yes	Yes
Atkin, 1996 UK/Ireland	Yes	NR	Yes	Yes	Yes
Barak, 2004	No, excluded patients without treatment charts	Yes (retrospective study)	Yes	Yes	Unclear if database/patient chart reviewer was blind to suicide status
Beauclair, 2007	Yes	Yes	NR	Yes	Yes
Bobes, 2003b	Unclear if the inception cohort (n=901) represented ALL patients hospitalized for an acute psychotic episode during the specified time period; unclear how sample narrowed down to 158	Unclear for the process of narrowing the sample from 901 to 158; low for LTFU among the 158	Yes	Yes	Unclear if the person(s) that administered the instruments were blinded
Bond, 2004	No, excluded patients: (1) didn't express goal of employment; (2) were noncompliant with medications; (3) didn't complete baseline interview; (4) discontinued early; (5) switched medications during the study	Withdrawals not reported	Yes	Yes	Unclear; no information about how the Vocational Placement Scale was administered

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Ascher-Svanum, 2004 US-SCAP Study Interim Results	Yes	Yes	Fair	
Ascher-Svanum, 2008	Yes	Yes	Fair	
Atkin, 1996 UK/Ireland	NR	Yes	Fair	
Barak, 2004	No; only commented regarding similarities in gender, age, distribution of diagnoses	Unclear	Fair	
Beauclair, 2007	Yes	Yes	Fair	
Bobes, 2003b	Partial; only covariates were baseline score and years since diagnosis	Yes	Poor	
Bond, 2004	No; only attempted adjustment for the few baseline differences in concomitant medication use, indicated adjustment didn't materially change the results, so presented unadjusted results	Yes	Poor	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Brown, 2005	No, excluded people who died during follow-up	There was differential loss to F/U Loss to F/U reported as 6/88 (6.8%) for ziprasidone; 27/103 (26%) for olanzapine	Yes	Yes	Unclear; chart review not duplicated
Buckman, 1999 United States	Unclear	NR	No	No	Unclear
Caro, 2002 Quebec	Yes	NR	Yes	Yes	Yes
Castro, 2007	Yes; see comment.	Yes; length of followup was significantly higher with clozapine than haloperidol or risperidone	Yes	Yes	Yes
Castro 2007	Unclear	Yes	Yes	Unclear	Unclear
Chen, 2008	Yes	NR	Yes	Yes	Yes

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Brown, 2005	No	Unclear	Poor: no adjusting for confounders; F/U interval unclear	retrospective, 2-group cohort
Buckman, 1999 United States	NR	Unclear	Poor	
Caro, 2002 Quebec	Yes	Yes	Fair	Between-group differences in age, gender, other characteristics
Castro, 2007	Yes	Yes	Fair	Authors note that patients may differ between treatment groups in their level of treatment resistance and
Castro 2007	Some	Yes	Poor	
Chen, 2008	Yes	Yes	Fair	It is not clear what % of patients included may have lost MediCal eligibility and were therefore lost to follow-up

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Citrome, 2004	Unclear Lower % of males in case group vs. control	NR	Yes	Yes	No Risk factors of BMI and activity level not assessed or controlled for. No assessment of baseline risk for diabetes and how that may have influenced choice of antipsychotic medication
Conley, 1999 United States	Yes	NR	Yes	Yes	Yes
Cooper, 2005 Cooper, 2007	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes	Yes; database tested for accuracy
Coulter, 2001 International	Unclear	NR	Yes	No	Unclear
de Haan, 1999	Yes	Yes (retrospective study)	No; not defined	No	No
de Haan, 2002	No; excluded 15 (6.2%) due to noncompliance and crossover	Withdrawals NR	yes	Yes	No; raters were unblinded

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Citrome, 2004	Partial	Yes	Fair	
Conley, 1999 United States	Yes	Yes	Fair	
Cooper, 2005 Cooper, 2007	Yes	Yes, 365-day study period	Fair	retrospective, 2-group cohort in pub #1 4 drugs compared in pub #2
Coulter, 2001 International	NR	Unclear	Poor	
de Haan, 1999	No; only commented regarding between-groups comparability for sex, age at admission and diagnosis	Yes	Poor	
de Haan, 2002	No; there was no information about between-groups comparability of baseline characteristics	Yes	Poor	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
De Hert 2008	Unclear; Historical cohort: Consisted of only 148/301 (49%) of patients with complete laboratory data. But, no significant differences between patients with and without complete laboratory data. Current cohort: No details provided on matching process. Significantly higher glucose in historic cohort (89 vs 84 mg/dl (*P*= 0.0055).	No; analysis excluded 22% overall (historic=21% vs current=37%)	Yes	Yes	Yes in "current" cohort of second-generation antipsychotics; unclear in historical cohort due to use of conversion factor for missing waist circumference measurements
Deliliers, 2000 Italy	Yes	NR	Yes	Yes	Yes
Devinsky, 1991 United States	Yes	NR	Yes	No	Unclear
Dinakar, 2002	Method NR, unable to determine.	Yes	Yes	Yes	Not reported if blind or independent assessment of outcomes.
Dolder, 2002	Yes	NA (pharmacy database with all records available)	Yes	Yes	Yes
Drew, 2002 Australia	Yes	NR	Yes	Yes	Yes

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
De Hert 2008	No and no information reported about comparability of baseline characteristics between groups of patients based on individual atypical antipsychotic agent	Yes	Poor	
Deliliers, 2000 Italy	NR	Unclear	Fair	
Devinsky, 1991 United States	Yes	Unclear	Fair	
Dinakar, 2002	No	Yes	Poor- no control for confounding factors, not reported if outcome assessors blinded or independent, unable to determine if selection was unbiased.	
Dolder, 2002	No, although baseline groups were similar for known confounders	Yes; 12 months	Fair	2-group cohort study; appears to be retrospective
Drew, 2002 Australia	NR	Yes	Fair	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Eberhard, 2006	NA (single-group study)	No (completers 166/223)	Yes	Yes	Yes (validated rating scale for TD)
Etminan, 2003 Ontario	No	NR	Yes	Yes	Yes
Faries, 2008	No Data on 28% of patients who switched from risperidone to an antipsychotic other than olanzapine were not included	Yes	Unclear if outcomes were prespecified for this study at start of RCT	Yes	"Responder day" measure of symptom severity at time of medication switch assumes linear change
Feldman, 2004 Buse, 2003	No- only included patients who maintained coverage with AdvancePCS were followed- those who discontinued coverage not analyzed; also excluded those missing information on sex or year of birth.	Yes (for those maintaining coverage)	Yes	Yes	Not reported if independent assessment of outcomes (but outcome was new prescription, so may be objective)
Fuller, 2003	Yes	NR	Yes	No	Yes
Ganguli, 2001	Yes- consecutive patients	Not reported	Yes	Yes	Not reported if independent assessment of outcomes (outcome was weight gain from chart review, objective, but several sources used, and judgment made about which of multiple weights recorded to use)

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Eberhard, 2006	NA (single-group study)	Yes: 5 years	Fair	this is an observational study of AE only (not efficacy); single-group cohort
Etminan, 2003 Ontario	Yes	NR	Poor	Diabetic events NR for 266 patients (reason NR)
Faries, 2008	Yes	Yes	Fair	
Feldman, 2004 Buse, 2003	Yes	Yes	Fair	
Fuller, 2003	Yes	Yes	Fair	
Ganguli, 2001	No	Yes (4 months)	Fair	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Gianfrancesco, 2002 United States	Yes	NR	Yes	No	Yes
Gianfrancesco, 2003a United States	Yes	NR	Yes	No	Yes
Gianfrancesco, 2003b United States	Yes	NR	Yes	No	Yes
Gianfrancesco, 2006	Yes	None	Yes	Yes	Yes
Gianfrancesco, 2006 (Hospitalization Risks in the Treatment of Schizophrenia)	Yes	NA (retrospective; only patients with data were analyzed)	Yes	Yes	Unclear, don't know reliability of the database
Gibson, 2004	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes, from Medicaid data	Unclear, don't know reliability of the database
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Yes	Yes	Yes	No	Unclear
Hagg, 1998 Sweden	Yes	NR	Yes	Yes	Yes
Haro, 2008	Yes	No 58.2% included	Yes	Yes	Yes

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Gianfrancesco, 2002 United States	Yes	Yes	Fair	
Gianfrancesco, 2003a United States	Yes	Yes	Fair	
Gianfrancesco, 2003b United States	Yes	Yes	Fair	
Gianfrancesco, 2006	Some	Yes	Fair	
Gianfrancesco, 2006 (Hospitalization Risks in the Treatment of Schizophrenia)	Yes	Unclear; mean treatment episode duration NR	Fair	
Gibson, 2004	No, there were many baseline differences, but clinical significance of the differences was unclear	Yes, 1 year	Fair	retrospective, 3-group cohort
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Yes	Yes	Fair	
Hagg, 1998 Sweden	No	N/A, cross-sectional study	Fair	
Haro, 2008	Yes	Yes	Fair	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Haukka 2008	Yes	Yes (retrospective study)	Yes	Yes	Yes
Hedenmalm, 2002	Yes	Yes (retrospective study)	Yes	Yes	Not stated if blinded or independent assessment of outcomes
Henderson, 2000 United States	Yes	NR	Yes	Yes	Yes
Henderson, 2005	Unclear; only information about sampling frame was observation period	NA (retrospective; only patients with data were analyzed)	Yes	Yes	Unclear, don't know reliability of the research psychiatrist in determining cause of death from autopsy reports and medical records
Hennessy, 2002	Not clear	Yes (retrospective study)	Yes	Yes	Not reported if independent assessment of outcomes
Herceg 2008	Not clear	Yes (retrospective study)	Yes	Not clear	Not clear
Ho, 1999	Unclear	No	Yes	Yes for group in the Longitudinal Study of Recent-Onset Psychosis, No for others	unclear, blinding NR

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Haukka 2008	Yes	Yes	Good	
Hedenmalm, 2002	No	Yes	Fair	
Henderson, 2000 United States	Yes	Yes	Fair	
Henderson, 2005	NA (single-group study)	Yes, 10 years	Poor	
Hennessy, 2002	Yes	Yes	Fair	
Herceg 2008	Some	Yes	Fair	
Ho, 1999	Partially, ANCOVA analysis was done to assess impact of differences at baseline in EPS, GAS, and QOL measures but other confounders not assessed.	Yes	Poor	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Hodgson, 2005	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes, from pharmacy records	Unclear
Honigfeld, 1996 United States	Yes	NR	Yes	Yes	Yes
Hrdlicka 2009	Unclear; eligibility required "medical record quality sufficient to evaluation the patient" and no information reported on comparison between patients with and without "sufficient record quality"	No; 57/109 (52%) did not complete the 6-week study period	Yes	Yes	Yes
Javitt, 2002	Unclear; indicates that data was obtained but doesn't indicate how	No loss to follow-up	Yes	No	No
Jerrell, 2007	NA (single-group study)	NA (retrospective; only patients with data were analyzed)	Yes	Yes	Yes
Jeste, 1999 United States	Yes	NR	Yes	Yes	Yes

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Hodgson, 2005	Yes	Unclear: study interval 1994-2001 but unclear if all three groups had same median observation period	Fair	retrospective, 3-group cohort
Honigfeld, 1996 United States	NR	Yes	Fair	
Hrdlicka 2009	No	No - 6 weeks	Poor	
Javitt, 2002	Yes	Yes	Fair	
Jerrell, 2007	NA (single-group study)	Unclear (F/U 3 years); for vascular outcomes longer F/U would be more useful	Fair	this is an observational study of AE only (not efficacy); single-group cohort (retrospective)
Jeste, 1999 United States	Partial: univariate regressions for baseline scores, age race, education, neuroleptic type, and daily dose on risk of TD. Subjects were matched for age, diagnosis, and length of neuroleptic exposure at study entry.	Yes	Fair	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Joyce, 2005	No, multiple exclusions applied depending on data most available.	None	Yes	Yes	Yes
Kane, 1993 United States	No	NR	Yes	Yes	Yes
Karagianis, 2009	Yes	Yes	Yes	Yes	No Interrater reliability not assessed. Open label - possible rater bias
Kasper, 2001	No; selected patients in reverse chronological order with 33 from each center; also only included data from centers that completed data collection and verification by a certain date	Yes (retrospective study)	Yes	No	Unclear; blinding NR
Kilzieh, 2008	Yes	Yes	Yes	Yes	Yes
Kim, 2008 (Effectiveness…)	Yes	Not reported	Yes	Yes	Yes

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Joyce, 2005	No	Yes	Poor	
Kane, 1993 United States	No and there were nonsignificantly more females (38% vs 24%) and schizoaffective patients (17% vs 8%) in control group and clozapine-treated patients were significantly older (32.4 vs 26.4 years) and had significantly longer exposure to neuroleptics at baseline (6.4 vs 2.3 years),	Yes	Poor	Between group differences in gender and diagnosis
Karagianis, 2009	Yes	Yes	Fair	More than half of included patients were using more than 1 antipsychotic medication concurrently
Kasper, 2001	Yes	Yes	Fair	
Kilzieh, 2008	Yes	Yes	Good	
Kim, 2008 (Effectiveness…)	No analysis of treatment visit frequency as a potential confounder. Frequency for RLAI group was every 2 weeks; oral was monthly	Yes	Fair	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Kim, 2008 (Time…)	Yes	Yes	Yes	Yes	Interrater reliability unclear
Koller, 2003	Yes	Yes	Yes	Yes	Not reported if independent assessment of outcomes.
Kopala, 2005	Unclear	No (49% drop-out at 2 years)	yes	Yes	Yes
Koro, 2002a	Yes	Yes (retrospective study)	Yes	Yes	Not reported if independent assessment of outcomes
Koro, 2002b	Yes	Yes	Yes	Yes	Not reported if independent assessment of outcomes.
Kozma, 2004 (poster) United States	Yes	NR	Yes	Yes	Yes
Kraus, 1999	Yes	Not reported	Yes	Yes	Not reported if independent assessment of outcomes (but outcome was weight, so may be objective)
Lambert, 2005	Yes; baseline data similar between groups	NA (retrospective; only patients with data were analyzed)	Yes	Yes	Unclear: 2 authors examined charts without blinding, but did have high inter-rater reliability
Lambert, 2006	Yes	None	Yes	Yes	Yes
Lambert, 2005	No, excluded patients that were not continuously eligible for Medi-Cal benefits	Yes: 5.4% at 24 weeks, 20.1% at 52 weeks	Yes	Yes	Yes

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Kim, 2008 (Time…)	Yes	Yes	Fair	
Koller, 2003	No- descriptive summary statistics only.	Yes	Fair	
Kopala, 2005	No	Yes	Poor	
Koro, 2002a	Yes	Yes (3 at least months)	Fair	
Koro, 2002b	Yes	Yes (mean 5.2 years)	Fair	
Kozma, 2004 (poster) United States	Yes	Unclear	Fair	
Kraus, 1999	No	4 weeks- not sure	Poor: unclear if all patients analyzed at all time points (no info on dropouts), no control for confounding factors.	
Lambert, 2005	No, although baseline groups were similar for known confounders	Yes, 18 months	Fair	Two-group cohort; retrospective
Lambert, 2006	Yes	Yes	Good	
Lambert, 2005	No	Yes	Poor	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Lee, 2002 United States	Yes	NR	Yes	Yes	Yes
Leslie, 2004	Not clear	Yes (retrospective study)	Yes	No	Not reported if blind or independent assessment of outcomes.
Lieberman, 1992 Alvir 1993 United States	Yes	NR	No	No	Unclear
Lin, 2006	Yes	Unclear	Yes	Yes	Unclear; 2 senior psychiatrists (first and second authors) verified data but no information provided about inter-rater reliability or overall reliability
Lindstrom, 1989	NA (single-group study)	Yes (attrition 3/96)	Yes	No	Unclear

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Lee, 2002 United States	Partial: Adjusted for age, sex, geographic region, diagnosis, hypertension, heart disease, and length of AP therapy. Did not adjust for dose.	Yes	Fair	79% of patients were only prescribed the index antipsychotic during the study period.
Leslie, 2004	No	Yes? (3 months)	Poor- No control for confounding factors, not reported if outcome assessor blinded, definition of outcomes and ascertainment techniques not adequately described, unable to determine if selection was unbiased.	
Lieberman, 1992 Alvir 1993 United States	Yes	Yes	Fair	
Lin, 2006	Yes	Yes	Fair	
Lindstrom, 1989	NA (single-group study)	Yes, 13 years	Fair-poor	Single-group cohort, retrospective; unclear how outcomes were ascertained

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Lindstrom, 2007	Yes	Yes	Yes	No	Unclear
Lublin, 2003	Yes	None	Yes	No	Unclear
Lucey, 2003	Unclear. 396 patients charts reviewed, but selection of these not stated	Yes (retrospective study)	Yes	Yes	Yes
Lund, 2001 United States	Yes	NR	Yes	Yes	Yes
Mladsi 2004 Fair	Unclear	NR	Unclear	Yes	Yes
McIntyre, 2003 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Yes	NR	Yes	No	Unclear
Medved 2009	Unclear	Yes	Yes for metabolic features; no for metabolic syndrome	Yes	Yes

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Lindstrom, 2007	Partial	Yes	Poor	
Lublin, 2003	No	12 weeks	Poor	
Lucey, 2003	Partially, analysis took into account mean dose and center.	Yes, for the outcome measure of time to discharge	Fair	
Lund, 2001 United States	Yes	Yes	Good	
Mladsi 2004 Fair	Yes	Yes	Fair	
McIntyre, 2003 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Yes	Yes	Fair	
Medved 2009	Yes for age or duration of illness; higher baseline triglyceride levels for olanzapine (1.91 vs 1.41 mmol; *P*= 0.017), but none of the clinical features tested as predictors in logistic regression on metabolic syndrome before SGA admission was significant.	No-3 months	Fair	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Meyer, 2002	No- excluded patients with incomplete data	Yes (retrospective study)	Yes	Yes	Not reported if independent assessment of outcomes
Miller, 1998	Not clear- identified patients from chart review.	Yes	Yes	Yes	Yes- blinded assessment of EPS
Modai, 2000 Israel	Yes	NR	Yes	Yes	Yes
Mohamed, 2009	Yes	NR	Yes	Yes	Yes
Moisan, 2005	Yes	None	Yes	Yes	Yes
Montes, 2003 Spain Sub-group Analysis from EFESO	Yes	Yes	Yes	No	Unclear
Mullins, 2008	Yes	Yes	Yes	Yes	Unclear
Naber, 2001	Method NR, unable to determine.	No (4% missing SWN data, 3% missing PANSS data)	Yes	Yes	Not blinded

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Meyer, 2002	No	Yes (one year)	Poor- may be biased selection, independent outcome assessment not reported, no control for potential confounding factors.	
Miller, 1998	Yes	Yes, but time period on medications varied (45.3 months clozapine, 13.4 months risperidone, 92.5 months conventional antipsychotics)	Fair	
Modai, 2000 Israel	Yes	Unclear	Fair	
Mohamed, 2009	Partial	Yes	Fair	
Moisan, 2005	Yes	6 months	Good	
Montes, 2003 Spain Sub-group Analysis from EFESO	Yes	Yes	Fair	
Mullins, 2008	Partial	Yes	Fair	
Naber, 2001	Yes	Yes	Fair	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Ollendorf, 2004 United States	Yes	NR	Yes	Yes	Yes
Opolka, 2003	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes	Unclear, don't know reliability of the database
Ostbye, 2004 United States	Yes	NR	Yes	Yes	Yes
Peacock, 1996 Denmark	No	NR	No	No	Not clear
Pelagotti, 2004	Yes	None	Yes	No	Unclear
Perez 2008	Unclear; groups differed but did adjust (e.g., quetiapine group had significantly greater proportions of comorbid mood disorders, previous hospitalizations, lower proportions of first episode status, and higher mean Calgary Depression Scale (CDSS) scores)	No; 50% for quetiapine and 42% for risperidone	Yes	Yes	Yes

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Ollendorf, 2004 United States	Yes	Yes	Fair	
Opolka, 2003	Yes	Yes, 1 year	Fair	retrospective, 3-group cohort
Ostbye, 2004 United States	Partial: does not control for dose and duration of treatment	Yes	Poor	
Peacock, 1996 Denmark	NR	Yes	Poor	
Pelagotti, 2004	No	Minimal (4-7 months) for Primary outcome 72 months for secondary outcomes	Poor	
Perez 2008	Adjusted means analysis using ANCOVA performed for efficacy outcomes (i.e., adjusted for unspecified clinical relevant and unbalanced baseline variables); no adjustment for weight gain or rehospitalization, but neither demonstrated a significantly significant difference	Yes	Poor	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Peuskens 2009	Unclear; some differences in baseline disease history, e.g., lower proportion of "first antipsychotic prescription" with olanzapine than risperidone (18% vs 30%)	No, 33% in olanzapine group and 29% in risperidone group did not complete the study	Yes	No	Unclear whether weight was self-reported or measured and whether outcome assessor was blinded
Phillippe, 2005	Yes	No, n = 3470 at enrollment, n = 1574 at analysis	Not clearly	Survey	Not clear
Procyshyn, 1998	Yes	None (retrospective)	Yes	No	No; method of determining classification as "responder" from physician note NR; blinding of chart reviewer NR
Ray 2009	Yes	Yes	Yes	No; who ascertained NR	Unclear; use of blinded, independent assessment NR; reliability of assessments NR
Rascati, 2003	Yes, Used instrumental variables to adjust for differences	NA (retrospective study including persons with available data only)	Yes	Yes	Unclear, don't know reliability of the database
Reid, 1998 United States	Unclear	NR	Yes	No	Unclear
Remington, 2001	Unclear	None	Yes	No	No

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Peuskens 2009	No	Yes	Poor	
Phillippe, 2005	Yes	Yes	Fair	
Procyshyn, 1998	No	Yes	Fair	
Ray 2009	Yes	Yes	Fair	
Rascati, 2003	Yes, used instrumental variables	Yes, 365-day study period	Good	retrospective, 2-group cohort
Reid, 1998 United States	NR	Unclear	Poor	
Remington, 2001	No	Yes	Poor	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Ren, 2006	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes	Unclear, don't know reliability of the database
Rettienbacher, 2006	Unclear	Unclear	Yes	No	No
Sax, 1998	Method NR, unable to determine.	No	Yes	Yes	Not reported if blind or independent assessment of outcomes.
Schillevoort, 2001a	Yes	Yes	Yes	Yes	Not reported (outcome assessor not specified)
Schillevoort, 2001b	Yes	Yes (retrospective study)	Yes	Yes	Not reported if blind or independent assessment of outcomes.
Sernyak, 2002	Yes	Yes	Yes	Yes	Not reported (outcome assessor not specified)
Shajahan, 2009	Yes	N/A: Retrospective chart review	Yes	Yes	Probably OK. Investigators assigned CGI scores retrospectively based on medical record notes. Author states the validity of this method has been previously established.

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Ren, 2006	Yes	Yes, 6-month	Fair	retrospective, 2-group cohort
Rettienbacher, 2006	No	Unclear	Poor	
Sax, 1998	No	Yes	Poor- no control for confounding factors, not reported if outcome assessors blinded or independent, unable to determine if selection was unbiased.	
Schillevoort, 2001a	Yes	Yes	Fair	
Schillevoort, 2001b	Yes	Yes	Fair	
Sernyak, 2002	Yes	Not sure- 4-month period studied.	Fair	
Shajahan, 2009	Yes	Yes	Fair	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Sharif, 2000	Yes	None (retrospective)	Yes	No information about the method the research assistant used to "assess symptom domain response" when reviewing the charts	No; after filling out structured rating forms during chart review, same unblinded research assistant blacked out identifying in formation, randomly assigned "X" or "O" to the blacked out forms and gave to research psychiatrists for interpretation
Snaterse, 2000	Unclear if chart review included ALL potential patients during the specified time period	None (retrospective)	Yes	No	Unclear; blinding NR
Spivak, 1998 Israel	Yes	NR	Yes	Yes	Yes
Strassnig, 2007	Yes	None	Yes	Yes	Yes
Strous, 2006	Unclear; referrals from treating physicians and sampling frame time period NR	None	Yes	Yes	Unclear, details about weight measurement methods NR
Su, 2005	Not clear	Unclear - only states that 15 completed the study	Not clear	Yes	Unclear
Sumiyoshi 2004	Unclear; "on randomly assigned days, all patients who visited the mental health center were contacted" and ultimately, "clinical data were obtained from 116 subjects meeting the study criteria"	Yes	Yes	Yes	Yes
Swanson, 2004	Unclear: groups differed but did adjust	75% retention both groups over 3 years; unclear if varied between groups	Yes	Yes	Yes; had multiple ascertainment methods

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Sharif, 2000	No	Yes	Poor	
Snaterse, 2000	Yes; but no demographics	Yes	Fair	
Spivak, 1998 Israel	NR	Yes	Fair	
Strassnig, 2007	Some	Yes	Fair	
Strous, 2006	Some	No - 12 weeks	Fair	
Su, 2005	No	3 months	Poor	
Sumiyoshi 2004	Yes for length of treatment, gender, age and race	Yes	Fair	
Swanson, 2004	Yes	Yes (3 years)	Fair	Prospective, 2-group cohort

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Tadger 2008	Unclear; selection methods NR	Yes; 4/70 excluded from analysis of increase/decrease in BMI from risperidone/olanzapine groups	No	No	Unclear
Taylor, 2003	Unclear if sample of charts that were reviewed represent those of ALL potentially eligible charts; also excluded 2 charts with inadequate dosing information	None (retrospective)	Yes	No description of how "documented positive statement of treatment effectiveness" was defined	No, efficacy outcome very subjective and blinding NR
Taylor, 2005	Unclear	Yes	Yes	Yes	No
Taylor, 2008	Yes	N/A: Retrospective chart review	Yes	Yes	Yes
Taylor, 2009	Yes	Yes	Yes	Yes	Yes

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Tadger 2008	No	Yes	Poor	
Taylor, 2003	Yes	Yes	Fair	
Taylor, 2005	No	No - 6 months	Poor	
Taylor, 2008	Bivariate only	Yes	Fair	Unclear whether a patient that switched AAPs would occur multiple times in the analysis, potentially contributing discontinuation data to more than one drug.
Taylor, 2009	Insufficient. Matched on age and gender, but was not able to adjust for smoking; there were 3 lung cancer deaths in clozapine.	Yes	Fair	Unclear how meaningful the mortality difference is. In risperidone there were only 3 deaths (ages 45, 65, 81), so the 95%CI's for observed and expected mortality were large and overlapped with the clozapine mortality estimates.

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Tilhonen, 2006	Yes	None	Yes	Yes	Yes
Tiihonen 2009	Yes	Yes	Yes	Yes	Yes
Umbricht, 1994 United States	No	NR	Yes	Yes	Yes
Van Winkel 2008	Yes	Yes	Yes	Yes	Yes
Verma, 2001	No	Yes	Yes	Yes	No, unblinded raters
Voruganti, 2000	No, convenience sample probably does not represent all of the patients among the 600 that would meet inclusion criteria	No withdrawals reported.	No	Yes	Yes
Wang, 2002 U.S.	Yes	n/a	Yes	Yes	Yes
Weiser, 2000	Yes ("recruited randomly")	No withdrawals reported.	Yes	Yes	No- raters of ESRS not blinded; other assessments computerized
Wirshing, 2002	No- included only records with adequate laboratory data, and excluded those with a lack of compliance (excluded 63.6% of charts reviewed).	Yes (retrospective study)	Yes	Yes	Not stated if blinded or independent assessment of outcomes (but lab test, may be objective)
Yood 2009	Yes	Yes (retrospective study)	Yes	Unclear	Unclear

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Tilhonen, 2006	Yes	Yes	Good	
Tiihonen 2009	Yes	Yes	Good	
Umbricht, 1994 United States	Yes	Yes	Fair	
Van Winkel 2008	No, and BMI was significantly greater for aripiprazole than olanzapine (28.4 vs 23.5 kg/m^2; $P<0.05$)	No - 3 months	Poor	
Verma, 2001	No	Unclear, follow-up ended at discharge, but mean duration of inpatient stay not reported	Poor	
Voruganti, 2000	No, and there were baseline differences in disease severity (clozapine patients were sicker)	Yes	Poor	
Wang, 2002 U.S.	Yes	N/A (case-control)	Fair	
Weiser, 2000	Controlled for age only.	Yes	Fair	
Wirshing, 2002	Yes	Yes (tests within 2 1/2 years included)	Fair	
Yood 2009	Yes	Yes	Fair	

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Yu 2008	Yes	Yes	Yes	Yes	Unclear
Yu, 2009	Yes	N/A: Subjects were selected on minimum 1-year enrollment after prescription date	Yes	Yes	Yes
Zhao, 2002	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes	Unclear, don't know reliability of the database
Zhao, 2002	Yes	No withdrawals reported	No	Yes	No
Zhang 2007	Yes, recruited randomly	Yes	No; no specification of primary outcome variable or whether both endpoint BMI and BMI gain were pre-planned	Yes	Yes

Evidence Table 7. Quality assessment of observational studies in patients with schizophrenia

Author, year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality assessment	Comments
Yu 2008	Yes - propensity score matching	Yes	Fair	
Yu, 2009	Yes	Yes; followup fixed at 12 months by design	Good	
Zhao, 2002	Yes	Yes, 1 year	Fair	retrospective, 2-group cohort
Zhao, 2002	Yes	Yes	Fair	
Zhang 2007	Unclear; states "where there was a significance in ANOVA, the effect of age, sex, duration of illness and neuroleptic dose were tested by adding these variables to the analysis model as co-variate", but no mention of results of these tests of co-variate regarding impact on significance of difference in BMI and BMI change between clozapine and risperidone	Yes	Poor	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Altamura, 2003 Italy	Open RCT Single Center	Bipolar Disorder with or without comorbid Axis I diagnoses; partial or full remission (according to DSM-IV criteria) of any previous mood episode	Monotherapy Quetiapine 157.7 mg Other mood stabilizers Valproate 492.6 mg Lithium 675 mg Gabapentin 300 mg 12 months	NR
Amsterdam, 2005 United States	RCT DB	Inclusion- Outpatients ≥ 18 years old with a DSM IV Axis I diagnosis of BP I or BP II disorder and a current DSM IV Axis I diagnosis of MDE and HAM-D 17 ≥ 18 Exclusion- current alcohol or substance abuse, a history of alcohol or substance dependence within 3 months, non-response to fluoxetine therapy within the current MDE, or a prior sensitivity to fluoxetine or olanzapine. Pregnant or nursing, unstable medical condition, or a serum thyrotropin level ≥ 5 µIU/ml., any clinically significant cardiac disease, malignancy, central nervous system disorder , clinically significant hepatic or renal disease, use of chemotherapy, use of over-the-counter preparations (e.g., St. John's Wort), use of tranquilizers, barbiturates or other sedative and hypnotic medications.	8-week, fluoxetine monotherapy 10 -60mg daily, olanzapine monotherapy 5 -20mg daily, the combination of fluoxetine 10-40mg daily plus olanzapine 5-20mg daily, or placebo	Run in at least 7 days

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Altamura, 2003 Italy	Benzodiazepines (≤ 5 mg/day); other compounds to treat acute mood episodes	YMRS BPRS HAM-D CGI Rated every 2 months by psychiatrists blind to treatment group Data analyzed using ANOVA with repeated measures	Mean age=52.1 42.8% male Race nr
Amsterdam, 2005 United States	Lorazepam 0.5–2.0 mg or chloral hydrate 250–1500 mg	28-item HAM-D the Montgomery–Asberg Depression Rating Scale, and the Young Mania Rating Scale (YMR)	Mean age 40 years 28% male 86% white 8% black 6% Hispanic

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Altamura, 2003 Italy	Bipolar I Disorder=13 (46.4%) Bipolar II Disorder=15(53.6%)	NR/NR/28	nr/nr/nr
Amsterdam, 2005 United States	8 (22.2%) married, 15 (41.7%) single, and 13 (36.2%) separated or divorced. 69% a first- or second-degree relative with known or suspected depression, and 50% a first or second degree relative with known or suspected BP disorder.	41/36/36	14/4/36

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Altamura, 2003 Italy	Quetiapine=Mood Stabilizers in YMRS, BPRS, HAM-D and CGI scores (data nr)	NR
Amsterdam, 2005 United States	There was no statistically significant difference in efficacy among the treatment groups. The frequency of patients with a ≥ 50% reduction in baseline HAM-D 17 scores did not differ among treatment groups. Data graphically presented Significant reduction in the mean YMR score in the fluoxetine-treated patients over time (p = 0.008).	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Altamura, 2003 Italy	*Quetiapine vs mood stabilizers* Mean weight gain (kg): +1.08 vs +1.7; p=NS Sedation and constipation (# pts): 2 vs 0 Weight gain (# pts with ≥ 4 kg weight gain): 0 vs 2	Total withdrawals NR Withdrawals due to adverse events=0	
Amsterdam, 2005 United States	NR	Total with drawals14 (41%) 2 for AEs	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
AZ - D1447C0001 EMBOLDEN I - 2007	DB RCT Multicenter: 110 sites in Europe, Canada, and Asia	Male or female aged 18-65 with DSM-IV bipolar disorder, most recent episode depressed; HAM-D 17-item score of >=20; YMRS score <=12.	8 week acute treatment phase, 3 groups: Quetiapine immediate-release tablets: 300 mg/day vs 600 mg/day, administered once a day at bedtime. Lithium 300 mg, administered twice daily in morning and at bedtime. Placebo.	Washout 5 to 28 days depending on medication

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
AZ - D1447C0001 EMBOLDEN I - 2007	NR	MADRS total score: change from baseline to Day 57 MADRS total score response (patients with >=50% reduction from baseline at Day 57) MADRS total score remission (patients with MADRS total score <=12 at Day 57) Change from baseline to Day 57 in MADRS item 10 (suicidal thought), HAM-D total score, HAM-D Item 1 (depressed mood), CGI BP-S total score, and HAM-A total score CGI-BP-C at Day 57 Change in MOS-Cog score, total SDS score, and number of missed and underproductive workdays on SDS	Mean age 42.2 40.7% male 85.3% Caucasian 0.1% Black 14.4% Oriental

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
AZ - D1447C0001 EMBOLDEN I - 2007	Bipolar I disorder: 62.2% Bipolar II disorder: 37.8% >=4 mood episodes over past year: 5.7% Mean MADRS (SE): 28.3 (0.22) Mean HAM-D: 24.2 (0.12) Mean HAM-A: 18.2 (0.21) YMRS: 3.2 (0.7)	Screened NR Eligible NR 922 enrolled 802 randomized	Analyzed: 783

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
AZ - D1447C0001 EMBOLDEN I - 2007	Quetiapine 300 mg and 600 mg were both superior to placebo in improving MADRS total score at Day 57. Quetiapine 300 mg (N=255) vs quetiapine 600 mg (N=263) vs placebo (N=129) vs lithium (N=136); p-value compared with placebo: MADRS total score, LS mean change from baseline: -15.36 (p<0.001) vs -16.10 (p<0.001) vs -11.81 vs -13.60 MADRS response: 68.6% (p<0.05) vs 69.6% (p<0.01) vs 55.8% vs 62.5% MADRS remission: 69.8% (p<0.01) vs 70.3% (p<0.01) vs 55.0% vs 62.5% MADRS item 10 (suicidality), LS mean change from baseline: -0.59 vs -0.64 (p<0.05) vs -0.43 vs -0.49 HAM-D total score, LS mean change from baseline: -13.98 (p<0.001) vs -14.17 (p<0.01) vs -1.26 vs -1.36 HAM-A total score, LS mean change from baseline: -9.14 (p<0.001) vs -9.29 (p<0.001) vs -6.55 vs -7.72 CGI-BP-S score, LS mean change from baseline: -1.51 (p<0.01) vs -1.57 (p<0.01) vs -1.14 vs -1.40 CGI-BP-C response: 64.7% (p<0.01) vs 61.6% (p<0.05) vs 48.1% vs 51.1% SDS total score, LS mean change from baseline: -6.9 (p<0.05) vs -7.54 (p<0.01) vs -5.33 vs -7.00 MOS-Cog total score, LS mean change from baseline: 5.67 vs 6.34 (p<0.05) vs 4.64 vs 5.98	AE incidence; % of patients with an AE of mania or hypomania, or YMRS score >=16 on 2 consecutive assessments or at final assessment N patients with an AE of suicidality N patients with HAM-D Item 3 score >=3 Change at any time in lab values, vital signs, weight, waist circumference, EPS, physical exams, eye exams, and ECG

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
AZ - D1447C0001 EMBOLDEN I - 2007	8-week acute phase: Quetiapine 300 mg (N=260) vs quetiapine 600 mg (N=267) vs placebo (N=131) vs lithium (N=136), % of group: Somnolence: 18.1 vs 17.6 vs 3.8 vs 8.8 Dry mouth: 14.2 vs 15.0 vs 1.5 vs 7.4 Dizziness: 9.6 vs 11.2 vs 5.3 vs 4.4 Headache: 7.3 vs 8.6 vs 13.7 vs 9.6 Sedation: 6.2 vs 5.2 vs 1.5 vs 0.7 Constipation: 4.6 vs 7.9 vs 2.3 vs 2.9 Nausea: 3.8 vs 5.6 vs 7.6 vs 16.9 Diarrhea: 2.3 vs 2.6 vs 3.8 vs 6.6 Insomnia: 2.3 vs 1.1 vs 5.3 vs 8.8 Tremor: 0.8 vs 3.4 vs 0.8 vs 5.9 During a 26-52 week continuation phase (quetiapine vs placebo), AEs that occurred more commonly with quetiapine were headache, nasopharyngitis, diarrhea, somnolence, weight increase, dizziness, and dry mouth.	Total withdrawals NR. Withdrawals due to AE: 27 (10.4%) in Quetiapine 300 37 (13.9%) in Quetiapine 600 11 (8.4%) in placebo 12 (8.8%) in lithium	Study was not powered to detect treatment differences in continuation phase. Data from continuation phase was included here only for AEs.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
AZ - D1447C00144 - 2008	DB RCT Multicenter: 128 sites in 15 countries, Asia, Europe, Central/South America, U.S.A.	Open-label phase: Men and women aged 18+ with DSM-IV diagnosed bipolar I disorder with an acute manic, depressed, or mixed episode at enrollment, or had a past manic, depressed, or mixed episode within 26 weeks that had been treated with quetiapine continuously (not interrupted for more than 2 weeks); and had at least 1 additional manic, depressed, or mixed episode in the 2 year period prior to index episode. To be eligible for randomization, a patient had to be treated with quetiapine (300-800 mg/day) for at least 4 weeks during the open-label treatment phase; stabilized in remission (YMRS total score <=12) and MADRS total score <=12 during the last 4 weeks of open-label treatment.	Open-label treatment phase (4 to 24 weeks): oral quetiapine, 300-800 mg daily with target dose of 600 mg/day, N=2438. Randomized DB phase (up to 104 weeks, but terminated early). Quetiapine (N=404): 300-800 mg/day, mean dose 546 mg/day. Lithium (N=364): 600 mg to 1800 mg/day, mean serum concentration 0.63 mEq/L Placebo (N=404). Mean duration of treatment with quetiapine was 191 days; maximum 715 days. Mean duration of treatment with placebo: 118 days, maximum 569 days. Mean duration of treatment with lithium was 130 days, maximum 553 days.	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
AZ - D1447C00144 - 2008	NR	Time to recurrence of the following: a mood event; manic event; depressed event; all-cause discontinuation; recurrence of a mood event, manic event, and depressed event per rating scale criteria: YMRS total score; MADRS total score, CGI-BP score; PANSS-P total score. Time required to complete TMT Parts A and B; SDS total score, MOS-Cog score, and WPAI score.	Mean age 39.5 46.7% male 63.1% Caucasian 16.9% Other 14.9% Oriental 5% Black

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
AZ - D1447C00144 - 2008	Most recent episode Manic: 53.6% Depressed: 28.0% Mixed: 18.4% With rapid cycling course: 13.9% YMRS total score at enrollment, mean: 15.30 YMRS total score at randomization, mean: 3.77 MADRS total score at enrollment, mean: 13.14 MADRS total score at randomization, mean: 3.44	Screened NR Eligible NR 2438 entered open-label phase; 1226 enrolled in DB RCT	679 withdrew (from DB RCT phase). Lost to followup NR. 1172 analyzed.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
AZ - D1447C00144 - 2008	Hazard ratio (95% CI); p-value Q vs P: Quetiapine (n=404) vs. Placebo (n=404) L vs P: Lithium (N=364) vs placebo (n=404) Q vs L: Quetiapine (N=404) vs Lithium (N=364) Time to recurrence of a mood event: Q vs P: 0.29 (0.23, 0.38); p<0.0001 L vs P: 0.46 (0.36, 0.59); p<0.0001 Q vs L: 0.66 (0.49, 0.88); p=0.0050 Time to recurrence of a manic event: Q vs P: 0.29 (0.21, 0.40); p<0.0001 L vs P: 0.37 (0.27, 0.53); p<0.0001 Q vs L: 0.78 (0.53, 1.16); p=0.2264 Time to recurrence of a depressed event Q vs P: 0.30 (0.20, 0.44); p<0.0001 L vs P: 0.59 (0.42, 0.84); p<0.0037 Q vs L: 0.54 (0.35, 0.84); p=0.0055 Quetiapine vs placebo, difference in LS means (SE) YMRS total score: -0.8 (0.2); p=0.002 MADRS total score: -1.4 (0.3); p<0.001 CGI-BP Severity of Illness: -0.19 (0.05); p<0.0001 CGI-BP Global Improvement: -0.28 (0.09); p=0.0025 PANSS-P score: -0.2 (0.1); p=0.103 MOS-Cog: 1.1 (0.4); p=0.007 WPAI: absenteeism, and overall work impairment, p=NS Activity impairment: =-7.6 (2.6); p=0.004 Impairment while working: -6.3 (2.6); p=0.014 SDS total score: Quetiapine significantly (p=0.0011) improved patient's level of functioning between mood events compared with placebo	AEs; lab results; vital signs; weight; waist circumference; ECG results; physical exams including eye exams; EPS: SAS, BARS, AIMS; Assessments for suicidality, EPS, QT prolongations, diabetes, neutropenia, somnolence, and concomitant medications.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
AZ - D1447C00144 - 2008	Quetiapine vs placebo vs lithium, % of group: Headache: 8.9 vs 7.9 vs 11.5 Somnolence: 6.7 vs 4.2 vs 2.6 Insomnia: 6.4 vs 17.1 vs 12.4 Nausea: 4.5 vs 8.2 vs 12.7 Tremor: 3.0 vs 2.0 vs 7.4 Diarrhea: 2.7 vs 5.2 vs 6.2 Vomiting: 2.0 vs 3.0 vs 11.2 EPS: 4.0 vs 4.5 vs 9.1 Mean weight change: +0.63 vs -1.51 vs -0.92 kg	625 total withdrawals during DB RCT (378 due to a mood event; 247 for other reasons, mainly patient not willing to continue). 47 withdrawals due to AE during DB RCT; 14 (3.5%) in quetiapine 13 (3.2%) in placebo 20 (4.8%) in lithium	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
AZ - D144CC00004 - 2007	DB RCT Multicenter: 50 sites in USA	Male or female aged 18-65 with DSM-IV bipolar I disorder, most recent episode manic or mixed; patients who experienced rapid cycling were eligible. Must have had at least 1 bipolar manic or mixed episode in the prior 5 years: YMRS total score >=20 with score of >=4 on 2 of 4 of the following YMRS core items: irritability, speech, content, and disruptive/aggressive behavior; and CGI-BP-S score >=4 at randomization (Visit 2). Included both hospitalized and non-hospitalized patients.	Quetiapine ER monotherapy, flexible dose 400 to 800 mg per day (mean 603.8 mg) vs placebo administered QD in the evening. 3 weeks of treatment. Patients were hospitalized at randomization and for at least the first 4 days of treatment.	Washout up to 28 days
Barbini, 1997 Italy	RCT	This sample included 30 bipolar inpatients (12 men, 18 women) consecutively admitted to the Research Center for Mood Disorders for a manic episode, according to the DSM IV criteria. The severity of manic symptomatology was classified in stage II-III for all patients. All patients had been treated with lithium salts for at least six months before the beginning of the study.	Mean dose: clozapine 175 mg/day chlorpromazine 310 mg/day Duration: 3 weeks	NR/ NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
AZ - D144CC00004 - 2007	NR	Change from baseline (randomization, Visit 2) to each visit and to final visit (Visit 6) in YMRS total score; Change in TYMRS total score response (patients with >=50% reduction of YMRS); YMRS total score remission (patients with a YMRS total score <=12 at final visit (Visit 6) Change from baseline to final visit in CGI-BP-S CGI-BP-C at final visit. Proportion of patients at Visit 6 with CGI-BP-C of "much improved" or "very much improved" Change in YMRS items 5 Irritability, or item 9 Disruptive/aggressive behavior Change in MADRS total score, baseline to Visit 6	Mean age 40.8 60% male 47% Caucasian 47.7% Black 1% American Indian/Alaskan Native 0.6% Asian
Barbini, 1997 Italy	NR	Young Rating Scale of Mania (YRSM)	Mean age: 36.6 years 37% male Ethnicity NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
AZ - D144CC00004 - 2007	Quetiapine ER vs placebo, mean scores at baseline: YMRS: 28.8 vs 28.4 CGI-BP-S depression: 2.4 vs 2.4 CGI-BP-S mania: 4.5 vs 4.5 CGI-BP-S overall bipolar illness: 4.5 vs 4.5 MADRS: 14.3 vs 14.6 Current episode % manic: 57.7% vs 55.3% Current episode mixed: 42.3 vs 44.7% History of rapid cycling: 30.2% vs 32.7% Median years since bipolar diagnosis: 18 vs 17 Duration of present mania episode, weeks: 4 vs 4 Attempted suicide, %: 56.4 vs 5.72%	Screened NR Eligible NR Enrolled NR	Withdrawn NR Lost to f. Up NR Analyzed 308 for efficacy, 311 for safety.
Barbini, 1997 Italy	clozapine vs chlorpromazine: Duration of illness (years): 9.7(7.2) vs 13.3(6.8) Duration of lithium treatment (months): 21.9(24.3) vs 8.4(7.4) Duration of last euthymic period (months): 10.26(11.04) vs 34.3(44.1) YRSM total score: 38.3(4.2) vs 34.1(8.0)	NR/NR/30	3/NR/27

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
AZ - D144CC00004 - 2007	Quetiapine ER for 3 weeks was superior to placebo in reducing mania symptoms. Quetiapine ER (N=149) vs placebo (N=159), results at Week 3: YMRS LS mean change (SE): -14.34 (0.91) vs -10.52 (0.88); p<0.001 Proportion (%) with >=50% YMRS response: 55 vs 33.3%; p<0.001 Proportion (%) with YMRS remission (total score <=12): 41.6 vs 27.7%; p=0.006 CGI-BP-S overall LS mean change (SE) from baseline: -1.51 (0.11) vs -1.02 (0.11); p<0.001 CGI-BP-C overall, LS mean (SE): 2.58 (0.12) vs 3.18 (0.12); p<0.001 CGI-BP-C "much" or "very much improved", %: 53.7 vs 32.7%; p<0.001	Physical exams, lab values, vital signs, ECG; EPS measured by SAS, BARS, Incidence of treatment-emergent depression, and/or MADRS score >18 on 2 consecutive assessments or on final assessment; Weight change from baseline to Visit 6 >=7% weight increase Incidence of suicidality
Barbini, 1997 Italy	Clozapine vs chlorpromazine YMRS (clozapine showed better improvement): group effect: p=0.07 time effect: p<0.0001 time-group interaction: p<0.0001 Post-hoc comparison: after 2 weeks treatment: p=0.0001 after 3 weeks treatment: p=0.0096	Dosage records and treatment emergent symptoms (DOTES) EPS: Simpson-Angus Rating scale

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Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
AZ - D144CC00004 - 2007	Quetiapine ER (N=151) vs placebo (N=160), % of group: Sedation: 34.4 vs 7.5% Dry mouth: 33.8 vs 6.9% Somnolence: 16.6 vs 4.4% Other AEs reported by at least twice as many in quetiapine ER than placebo: constipation, dizziness, and increased weight. Weight increase >=7%: 5.1 vs. 0% EPS: 6.6 vs 3.8% Treatment-emergent depression: 1 in placebo Suicidal behavior/ideation: 1.3 vs 3.1%	Total withdrawals NR. Withdrawals due to AEs: 4 (2.6%) in quetiapine ER vs 4 (2.5%) in placebo.	
Barbini, 1997 Italy	Clozapine vs Chlorpromazine hypersialorrhea: 10(67%) vs 3(25%) sedation: 7(46%) vs 8(68%) WBC decrease: 8(53%) vs 0(0%) hypotension: 5(30%) vs 5(45%) EPSE: 1(7%) vs 7(56%)	NR	

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Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Bowden, 2005 Europe and Asia	RCT, DB, parallel, Multicenter	Eligible subjects were adult (≥ 18 years) inpatients (after day 7, patients could be discharged if investigator felt that was appropriate) hospitalized with a diagnosis of bipolar I disorder, current episode manic, according to the DSM-IV. All pts had experience at least 1 prior reliably documented manic or mixed episode. At screening and at randomization (7 days after screening), pts were required to have a score of at least 20 on the Young Mania Rating Scale (YMRS), including a score of at least 4 on 2 of the 4 double-weighted YMRS items (irritability, speech, content, and disruptive/aggressive behavior). A Clinical Global Impression-Bipolar Version (CGI-BP) Severity of Illness score for overall bipolar illness of at least 4 was also required.	Monotherapy Quetiapine uptitrated to 400 mg/d on day 4; could be adjusted up to 600 mg/d on day 5 and up to 800 mg/d thereafter (days 6-84) Lithium 900 mg/d (dose adjustments between days 5-84 at investigator's discretion) 12-weeks	NR/ medications known to be associated with withdrawal from treatment were tapered off (over approximately 1 week)

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Bowden, 2005 Europe and Asia	Medications prescribed for stable medical, non-psychiatric illnesses, oral contraceptives, and antihypertensive treatments (if stable dosage ≥1 month prior to randomization). Lorazepam allowed for agitation, not sedation. These sedative hypnotics allowed, 1 per day: Zolpidem, chloral hydrate, zopiclone, zaleplon. Anticholinergic medications allowed only for EPS.	YMRS, PANSS, MADRS, CGI and CGI-BP assessed on days 1, 4, 7, 14, 21, 28, 42, 56, 70, 84. Global Assessment Scale (GAS) assessed on days 1, 21, and 84. Primary efficacy endpoint: change in YMRS at day 21 Secondary efficacy endpoint: change in YMRS at day 84, and changes in other scores on days 21 and 84	Mean age: 39.0 years 57.7% male Ethnicity NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Bowden, 2005 Europe and Asia	Mean baseline scores, quetiapine (N=107) vs lithium (N=98) vs placebo (N=97) YMRS: 32.7 vs 33.3 vs 34.0 MADRS: 6.1 vs 6.3 vs 6.2 PANSS: 58.2 vs 58.0 vs 58.7 CGI-BP Severity of Illness score: 4.9 vs 4.9 vs 5.0	NR/NR/302	128 (42.4%) withdrawn/ 7 (2.3) lost to follow-up/ 300 analyzed

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Bowden, 2005 Europe and Asia	Quetiapine vs lithium (Li) vs placebo Change in mean YMRS scores from baseline at day 21: -14.62 vs -15.20 vs -6.71 (p=NS, quet vs Li; p<0.001 for quet vs placebo and Li vs placebo) at day 84: -20.28 vs -20.76 vs -9.00 (p=NS, quet vs Li; p<0.001 for quet vs placebo and Li vs placebo) % of patients with a YMRS response rate (defined as a >=50% reduction in score) : at day 21: 53.3% vs 53.1% vs 27.4% (p=NR, quet vs placebo; p<0.001 for quet vs placebo and Li vs placebo) at day 84: 72.0% vs 75.5% vs 41.1% (p=NR, quet vs placebo; p<0.001 for quet vs placebo and Li vs placebo) Change in CGI-BP scores from baseline (p<0.001 for quet vs placebo and Li vs placebo both days) : at day 21: -1.84 vs -1.41 vs -0.66 at day 84: -2.20 vs -2.18 vs -0.89 Change in PANSS scores from baseline, quet vs placebo (lithium data given only as "similar significant effects were seen with Li vs pla") : Total PANSS score, at day 21: -8.71 vs -2.12, p<0.001 at day 84: -11.78 vs -1.04, p<0.001 PANSS Positive subscale, day 21: -4.93 vs -1.55, p<0.001 at day 84: -6.85 vs-1.48, p<0.001 Change in MADRS score from baseline : at day 21, quet vs placebo: -1.55 vs -0.05, p=0.15 at day 84: quet -1.49 vs lithium -1.83 vs placebo +1.21 (p=0.002 for quet vs pla; p=0.001 for Li vs pla) Change in Global Assessment Scale (GAS) from baseline, quet vs placebo: at day 21: 17.96 vs 5.59, p<0.001 and day 84: 26.35 vs 9.26, p<0.001 Completers at day 21: 90.7% vs 85.7% vs 69.1% at day 84: 67.3% vs 68.4% vs 36.1%	Vital sign measure measurements at days 1, 4, 7, 14, 21, 28, 42, 56, 70, and 84 Safety evaluations were based on reports of AEs, trough serum concentrations, concomitant medication records, vital signs, weight, and clinical lab parameters. EPS assessed with AE reporting, Simpson-Angus Scale (SAS), and the Barnes Akathisia Rating Scale (BARS) Treatment-emergent depression, defined a priori as MADRS score >=18 and an increase of >=4 from baseline on any 2 consecutive post-baseline visits, or at the final study visit, was monitored.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Bowden, 2005 Europe and Asia	Quetiapine vs lithium vs placebo Dry mouth: 24.3% vs 6.1% vs 2.1% Somnolence: 19.6% vs 9.2% vs 3.1% Weight gain: 15.0% vs 6.1% vs 1.0% Dizziness: 12.1% vs 7.1% vs 2.1% Insomnia: 9.3% vs 16.3% vs 20.6% Headache: 7.5% vs 12.2% vs 4.1% Asthenia: 6.5% vs 4.1% vs 1.0% Depression: 5.6% vs 1.0% vs 1.0% Tremor: 5.6% vs 18.4% vs 4.1% Diarrhea: 4.7% vs 5.1% vs 4.1% Weight loss: 1.9% vs 6.1% vs 1.0% Anorexia: 0.9% vs 9.2% vs 4.1% Nausea: 0.9% vs 6.1% vs 2.1% Vomiting: 0.9% vs 6.1% vs 2.1% Akathisia: 0.9% vs 3.1% vs 6.1% EPS-related AEs, quet vs placebo: 13.1% vs 9.3% Mean weight gain, observed cases (LOCF) from baseline: 3.3 (LOCF: 2.6) vs 1.0 (LOCF: 0.7) vs 0.3 (LOCF: -0.08) kg p<0.001 for quet vs placebo and p=NS for lithium vs placebo Emergent depression, day 84: 5.6% vs 3.1% vs 8.4%, p=NS for comparisons Prolactin concentration (in micrograms/L) change from baseline: -18.4 vs -17.3 vs -13.2 SAS and BARS scores: no significant difference in change from baseline for quet vs placebo	Total withdrawals: 42.4% (128/302) Quetiapine vs lithium vs placebo Total withdrawals by drug group: 32.7% vs 31.6% vs 63.9% Withdrawals due to AEs: 6.5% vs 6.1% vs 4.1%	Both groups got blood testing to keep blinding valid

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Bowden, 2005 Paulsson, 2003 (poster) United States	RCT, DB Multicenter Parallel	Male and female (≥ 18 years of age) with a DSM-IV diagnosis of bipolar I disorder and at least one prior manic or mixed episode; hospitalized with a manic episode (eligible for discharge after Day 7); YMRS score ≥ 20, including score ≥ on 2 of the core YMRS items of Irritability, Speech, Content, and Disruptive/Aggressive Behavior; CGI-BP Severity of Illness score ≥ 4	Quetiapine (QTP): 100, 200, 300, and 400 mg/d on Days 1, 2, 3, and 4, respectively; 200-600 mg/d on Day 5; 200-800 mg/day on Days 6-84 Lithium: 900 mg/d on days 1-4; dose adjustments on Days 5-84 to achieve trough serum concentrations of 0.6-1.4 mEq/L Placebo (PBO) Duration: up to 12 weeks	NR/NR
Brown 2008 USA - Texas	DB RCT Single Center	Bipolar 1 or 2, alcohol abuse or dependence within 14 days; 18 to 55years old; no changes in concomitant psychiatric meds in last 7 days	Adjunctive Quetiapine vs. placebo 12 weeks	None

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Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Bowden, 2005 Paulsson, 2003 (poster) United States	Previously prescribed medications for stable medical conditions Zolpidem tartrate, chloral hydrate, zopiclone, or zaleplon for insomnia Lorazepam (for agitation) titrated down from 6 mg/d at screening to 1 mg/d by Day 11 and not permitted after Day 14	Primary: Change from baseline in YMRS score at Day 84 Secondary (assessed at Day 21 and Day 84): YMR response rate (percent of patient ≥ 50% improved); YMRS remission rate (percent of patients with YMRS score ≤ 12); % of patients maintaining YMRS response of remission; CGI and CGI-BP response rate (% of patients rated as "much" or "very much" improved from baseline on Global Improvement scale); Change from baseline in CGI and CGI-BP severity of illness scores, PANSS scores; MADRS score, GAS score	Mean age=39.3 42.3% female Ethnicity NR
Brown 2008 USA - Texas	Yes	HAM-D, YMRS, PACS, rate of drinking, assessed at baseline, weeks 1, 2, 4,6,8,10,12	Mean age 38.5 years % male 62.7 % white 61 % African American 27.5 % Hispanic 9 % other 3

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Bowden, 2005 Paulsson, 2003 (poster) United States	Mean weight (kg): 63.9 Mean BMI (kg/m2): 23.4 Mean YMRS total score: 33.3 Manic, moderate: 31% Manic, severe: Without psychotic features: 41.3% With psychotic features: 27.7%	NR/NR/302 (quetiapine n=107; placebo n=97; lithium n=98)	Withdrawn=128 (42.7%)/Lost to fu=7 (2.3%)/analyzed=300 (quetiapine n=107; placebo n=95; lithium n=98)
Brown 2008 USA - Texas	% bipolar I 49 % bipolar II 51 % alcohol dependent 97 % alcohol abuse 3	NR/NR/115	NR/13 LTF/102

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Bowden, 2005 Paulsson, 2003 (poster) United States	Quetiapine vs placebo Lithium vs placebo Mean change in YMRS Day 21 -14.62 vs -6.71; p<0.001 -15.2 vs -6.71; p<0.0001 Day 84 -20.28 vs -9; p<0.001 -20.76 vs -9, p<0.001 Response/remission for quetiapine vs placebo (p<0.001 for all comparisons) (estimated from graph) Day 21 YMRS response: 54% vs 28% YMRS remission: 47% vs 22% CGI-BP response: 63% vs 31% Day 84 YMRS response: 73% vs 43% YMRS remission: 70% vs 35% CGI-BP response: 73% vs 39% PANSS Total Score: Quetiapine > placebo in mean reductions at Days 21 and 84 (p<0.001) (data nr) PANSS subscales at Day 21 (p<0.001 for all comparisons (estimated from graph) Positive: -4.9 vs -1.5 Activation: -3.6 vs -0.9 Aggression risk: -4.2 vs -1.4 MADRS mean reductions: QTP > PBO at Day 21 (p=0.015) and Day 84 (p=0.002) GAS mean increases: QTP > PBO at Days 21 (p<0.001) and 84 (p<0.001)	NR
Brown 2008 USA - Texas	Quetiapine vs. placebo Baseline(SD)/exit(SD) HAM-D 19.8(6.9)/11.1(7.4) vs. 20(5.9)/12.6(7.7) YMRS 9.5(7)/5(3.8) vs. 12.3(5.8)/6.9(5.8) PACS 19.6(7.1)/12.6(7.8) vs. 18.3(6.6)/11.4(9.1) Drinking d/wk 3.3(2.2)/2.1(2.1) vs. 3(1.6)/1.7(2.1) Median drinks/wk 15/6 vs. 17/3 Heavy drinking Days/wk 2.4(2.3)/1.2(1.7) vs. 2.1(1.6)/1(1.6)	AIM, SAS and BAR, AEs were assessed at study visits

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Bowden, 2005 Paulsson, 2003 (poster) United States	Treatment-emergent depression (MADRS score of ≥ 18 with an increase from baseline of ≥ 4 at any 2 consecutive assessments or at last observation): QTP=5.6% vs PBO=8.4%; p=nr Mean change in weight (day 84) (observed cases) (kg): QTP=+3.3 vs PBO=+0.66, p=nr QTP vs PBO Dry mouth: 26 (24.3%) vs 2 (2.1%), p<0.0001 Somnolence: 21 (19.6%) vs 3 (3.1%), p=0.0003 Weight gain: 16 (15.0%) vs 1 (1.0%), p=0.0002 Dizziness: 13 (12.1%) vs 2 (2.1%), p=0.0004 Insomnia: 10 (9.3%) vs 20 (20.6%), p=0.0292 Headache: 8 (7.5%) vs 4 (4.1%), ns Asthenia: 7 (6.5%) vs 1 (1.0%), ns Depression: 6 (5.6%) vs 1 (1.0%), ns Tremor: 6 (5.6%) vs 4 (4.1%), ns EPS-related adverse events: 13.1% vs 9.3%, ns SAS and BARS mean changes: QTP=PBO, ns (data nr) Akathisia: 0.9 vs 6.2%, ns	QTP vs PBO Total withdrawals: 35 (32.7%) vs 62 (63.9%), p<0.0001 Withdrawals due to adverse events/concurrent illness: 7 (6.5%) vs 4 (4.1%), ns	
Brown 2008 USA - Texas	Quetiapine vs. placebo % Sedation 24 vs. 16 Dizziness 22 vs. 0 Dry mouth 18 vs. 6 Fatigue 8 vs. 4 Indigestion 6 vs. 0	Total withdrawals or those due to AEs are not reported.	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Calabrese, 2005 Cookson, 2007 (NNT's for response/remission; time to response/remission) Endicott, 2007 (Q-LES-Q results) Hirschfeld, 2006 (HAM-A results) United States BOLDER 1	RCT, DB Multicenter Parallel	Adults with a DSM-IV diagnosis of bipolar I or bipolar II disorder (with or without rapid cycling); HAM-D17 ≥ 20; YMRS ≤ 12	Quetiapine 600 mg (QTP600) Quetiapine 300 mg (QTP300) Placebo	NR/NR
Cutler; Ortho - NCT00299715-2007 Lead investigator is in USA; country NOS	DB RCT Multicenter	Male or female subjects aged 18-65 with DSM-IV diagnosed Bipolar I Disorder, most recent episode manic or mixed; with history of at least 1 documented manic or mixed episode requiring medical treatment within 3 years before screening; and having a total score >=20 on the YMRS at screening and baseline.	3-week DB phase, 4 groups: Oral paliperidone ER: 3, 6, or 12 mg/day Placebo For all groups, 2 capsules were taken orally once daily. Subjects were hospitalized for first 7 days of DB phase.	7 day washout

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Calabrese, 2005 Cookson, 2007 (NNT's for response/remission; time to response/remission) Endicott, 2007 (Q-LES-Q results) Hirschfeld, 2006 (HAM-A results) United States BOLDER 1	Treatment with other psychoactive drugs prohibited	Primary: Change from baseline to final assessment in MADRS score Secondary: Response rate (≥ 50% decrease in MADRS); Remission rate (MADRS score ≤ 12); mean change from baseline to last assessment in HAM-D, CGI, PSQI, Q-LES-Q	Mean age=37.4 58.1% female Ethnicity NR
Cutler; Ortho - NCT00299715-2007 Lead investigator is in USA; country NOS	NR	YMRS, GAF, CGI-BP-S, PANSS, Sleep VAS, SF-36; assessed at baseline and Day 21, or upon early withdrawal from study. Change from baseline to endpoint (LOCF) in YMRS and GAF were the primary outcomes.	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Calabrese, 2005 Cookson, 2007 (NNT's for response/remission; time to response/remission) Endicott, 2007 (Q-LES-Q results) Hirschfeld, 2006 (HAM-A results) United States BOLDER 1	DSM-IV diagnosis Bipolar I disorder=66.9% Bipolar II disorder=33.1% Rapid cycling=21.1% Mean MADRS score=30.4% Mean HAM-D score=24.6% Mean YMRS score=4.9%	838/NR/542	216 (39.8%) withdrawn/lost to fu nr/analyzed=511 (QTP600=170, QTP300=172, Placebo=169)
Cutler; Ortho - NCT00299715-2007 Lead investigator is in USA; country NOS	NR	NR/NR/467	465 analyzed

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Calabrese, 2005 Cookson, 2007 (NNT's for response/remission; time to response/remission) Endicott, 2007 (Q-LES-Q results) Hirschfeld, 2006 (HAM-A results) United States BOLDER 1	QTP600 vs QTP300 vs Placebo MADRS mean change (week 8): -16 vs -16 vs -10 (estimated from graph), p<0.001 for both Week 8 response (% patients): 58% vs 58% vs 36%, p<0.001for both, NNT=5 for both Median time to response (days): 22 vs 22 vs 36; p<0.001 Week 8 remission (% patients): 53% vs 53% vs 28%, p<0.001 for both, NNT=5 for both Median time to remission (days): 27 vs 29 vs 65; p<0.001 HAM-D mean change (week 8 estimated from graph): -1.6 vs -1.5 vs -1.2, p<0.001 for both Mean change in CGI (study end): -1.66 vs -1.63, vs -0.95, p<0.001 for both Least squares mean change from baseline in Q-LES-Q percentage maximum: 18.1 vs 21.5 vs 12.1, p<0.001 for both HAM-A total score mean change: -10.8 vs -9.9 vs -6.7; p<0.001 for both HAM-A total score subgroup analyses based on Bipolar Disorder Type (pooled dose groups): Bipolar I: -10.4 vs -5.1, p<0.001 Bipolar II: -9.8 vs -9.0, p=NS	Proportion of patients who met criteria for treatment-emergent mania (YMRS score ≥ 16 on two consecutive visits or at final assessment; incidence of adverse events; incidence of EPS, including akathisia, assessed by direct reporting and using SAS and BARS
Cutler; Ortho - NCT00299715-2007 Lead investigator is in USA; country NOS	YMRS score decreased in all treatment groups; mean (SD) change, placebo / paliperidone ER 3-mg / 6-mg / 12-mg: -9.9 (10.22) / -9.6 (11.30) / -11.7 (10.04) / -13.9 (9.19); p=0.005 comparing 12-mg to placebo. P=NS comparing 3-mg or 6-mg to placebo. Percentage of severely ill patients decreased significantly in paliperidone ER 12-mg compared with placebo (p=0.046) based on CGI-BP-S scores (results NR). Sleep quality improved in all groups; Sleep VAS mean (SD) increase, placebo / paliperidone ER 3-mg / 6-mg / 12-mg: 8.3 (36.28) / 12.6 (33.25)/ 17.6 (30.79) / 20.6 (33.93); p=0.034 comparing 6-mg to placebo; p<0.001 comparing 12-mg to placebo. No differences between any paliperidone ER group and placebo on GAF, percentage of YMRS responders, PANSS total score; PANSS positive or negative subscales, PANSS Marder factors, daytime drowsiness, or SF-36.	Clinical labs, vital signs, weight and BMI, ECGs, physical exams, rating scales for EPS, MADRS, and Scale for Suicidal Ideation. Follow-up safety assessment 1 week after Day 21 or early withdrawal from study.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Calabrese, 2005 Cookson, 2007 (NNT's for response/remission; time to response/remission) Endicott, 2007 (Q-LES-Q results) Hirschfeld, 2006 (HAM-A results) United States BOLDER 1	Treatment-emergent mania: 2.4% vs 3.5% vs 4.1%, ns Weight gain (kg): +1.6 vs +1.0 vs +0.2, ns SAS mean change: -0.1 vs -0.2 vs -0.3, ns BARS mean change: 0 vs -0.1 vs -0.1, ns Dry mouth: 73 (40.6%) vs 79 (44.1%) vs 14 (7.8%), p<0.0001 for both Sedation: 58 (32.2%) vs 53 (29.6%) vs 11 (6.1%), p<0.0001 for both Somnolence: 44 (22.4%) vs 49 (27.4%) vs 15 (8.3%), p<0.0001 for both Dizziness: 41 (22.8%) vs 30 (16.8%) vs 15 (8.3%), p=0.0002, p=0.0171 Constipation: 20 (11.1%) vs 21 (11.7%) vs 8 (4.4%); p=0.0288, p=0.012	Withdrawals due to adverse events: 47 (26.1%) vs 29 (16%) vs 16 (8.8%), p<0.001, p<0.0392	
Cutler; Ortho - NCT00299715-2007 Lead investigator is in USA; country NOS	Mania: 6% of placebo, 2-3% in paliperidone ER groups Prolactin-related AEs: 3 in paliperidone ER and 1 in placebo AEs that occurred in more than 5% of any paliperidone ER group, and >=3% more frequently than in placebo: headache, somnolence, dizziness, sedation, akathisia, dystonia, and dyspepsia. EPS were more frequent in any paliperidone ER group than placebo, and more frequent in paliperidone ER 12-mg than in the 3-mg or 6-mg groups. The % of subjects who used anticholinergic medications increased with dose: 9% in placebo and paliperidone ER 3-mg, 13% in 6-mg, and 28% in 12-mg. Increase in weight and BMI was greater with paliperidone ER (1.1kg, 0.4 kg/m2 in BMI) than placebo (0.2 kg, 0.1 kg/m2 BMI). No deaths occurred.	Total withdrawals NR; 29 (6.2%) withdrawals due to AE	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Harvey, 2007 USA	Randomized, DB cross-over	18-55 years old DSM-IV diagnosis of bipolar I disorder in partial or full remission and a Young Mania Rating Scale score <or= 8 Exclusion- use of sedating medications; current diagnosis of MDD, mania, hypomania, psychosis, dysthymia, or catatonic behaviors.	Risperidone-quetiapine sequence received 2 mg of risperidone with dinner and placebo with breakfast during period 1 and 100 mg of quetiapine with dinner and 100 mg with breakfast during period 2.	6-14 days between treatment periods
Hirschfeld, 2004 USA	RCT Multicenter Hospitalized ≥ 7 days	Men and women age 18 years or older who met DSM-IV criteria for bipolar I disorder, current episode pure mania; history of at least one prior documented manic or mixed episode that required treatment prior to screening; YMRS score ≥ 20 at screening and baseline evaluations; MADRS score ≤ 20 at the baseline evaluation	Monotherapy Risperidone 1-6 mg daily Placebo 3-week DB	3-day washout

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Harvey, 2007 USA	Yes if they were stable for the proceeding 8 weeks.	NA	Mean age 40.9 years 71% male 32% white 61% black 7% other
Hirschfeld, 2004 USA	Lorazepam ≤ 8 mg daily during washout and first 3 days of treatment; ≤ 6 mg daily during days 4-7; ≤ 4 mg daily during days 8-10 Antiparkinsonian medications allowed throughout the study	Primary: Mean change in YMRS Secondary: Other YMRS, CGI, MADRS, PANSS, GAS measurements Scales administered at screening, baseline, and on days 1, 3, 7, 14, and 21	Mean age=39 43.2% female 71.8% white

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Harvey, 2007 USA	DSM-IV diagnosis (patients) Hypomanic or manic episode: Partial remission: 1 (3.6%) Full remission: 3 (10.7%) Major depressive episode Partial remission: 1 (3.6%) Full remission: 19 (67.8%) Mixed episode in full remission: 2 (7.1%) Current or most recent episode in full remission: 2 (7.1%) Years since diagnosis: 10.0 YMRS total score: 2.9 MADRS total score: 5.6	NR/NR/30	2/NR/28
Hirschfeld, 2004 USA	Psychotic features present: 42.5%	337/NR/262 Risperidone n=134 Placebo n=125	132 (51%) withdrawn 4 (1.5%) lost to fu 246 (95%) analyzed

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Harvey, 2007 USA	see adverse events	Assumed to be patient reported, not specified
Hirschfeld, 2004 USA	Risperidone vs placebo YMRS mean change (mean points): -10.6 vs -4.8; p<0.001 YMRS response (% patients with ≥ 50% improvement): 43% vs 24%; p=0.006 YMRS remission (% patient with score ≤ 12): 38% vs 20%; p=0.007 CGI mean change (points): -1.1 vs -0.4; p<0.001 GAS mean change (points): 12.5 vs 5.5; p<0.001 PANSS total score mean change (points imputed from a graph): -10 vs -1.5; p<0.001 MADRS mean change (points estimated from a graph): -7.5 vs -8.1; p=NS	Extrapyramidal Symptom Rating Scale administered at days 7, 14, and 21 to measures movement disorders Other adverse events assessed by investigatory query

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Harvey, 2007 USA	Risperidone vs. Quetiapine Total AEs 18 vs. 36 at least 1 AE 14 vs. 25 p < 0.05 vs. risperidone Somnolence 9 vs. 24 p < 0.05 vs. risperidone Fatigue 4 vs. 6 Dry mouth 0 vs. 3 Headache 2 vs. 0 Carpal tunnel 1 vs. 0 Dystonia 1 vs. 0 Nausea 1 vs. 0 Blurred vision 0 vs. 1 Nasal congestion 0 vs. 1	Withdrawals 2 due to AEs 0	
Hirschfeld, 2004 USA	Manic reaction: 7.5% vs 4.8%; p=NS Death: 0 vs 2/125 (1.6%); p=NS Somnolence: 28% vs 7%; p<0.001 Headache: 14% vs 15%; p=NS Hyperkinesia: 16% vs 5%; p=NS Dizziness: 11% vs 9%; p=NS Dyspepsia: 11% vs 6%; p=NS Nausea: 11% vs 2%; p=NS Extrapyramidal Symptom Rating Scale (mean change) Total score: 0.6 vs 0; p=0.05 Parkinsonism subscale: 0.5 vs 0; p=0.05 Dystonia: 0.1 vs 0; p=NS Dyskinesia: 0 vs 0; p=NS	Risperidone vs placebo Total withdrawals: 44% vs 58%; p<0.05 Withdrawals due to adverse events: 8% vs 6%; p=NS	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Houston, 2009 United States and Puerto Rico	RCT, DB Multicenter (24)	Male or female outpatients 18-60 years old who had DSM-IV-diagnosed bipolar disorder with a current mixed episode, inadequate response (defined by 21-item HAM-D and YMRS total scores >=16) to divalproex for at least 14 days, with blood level of divalproex between 75-15 microg/mL	Divalproex plus olanzapine 15 mg/d initially, followed by flexible dosing (5-20 mg/d) Divalproex plus placebo. Target blood level of divalproex was maintained at 75 to 125 µg/mL. 6 weeks	Response to divalproex (blood levels 75 to 125 µg/mL) was determined during first phase (4-28 days; N=446). 202 with inadequate response were randomized to adjunctive olanzapine or placebo.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Houston, 2009 United States and Puerto Rico	Benzodiazepine permitted for ≤15 cumulative or ≤5 consecutive days. Thyroid hormone supplements permitted if subject had been on medication for at least 2 months and had serum TSH within normal range.	Primary efficacy: change from baseline to 6-weeks on 21-item HAM-D and YMRS. Secondary outcomes: time to partial response (at least 25% reduction on both HAM-D and YMRS total scores); time to response (at least 50% reduction on both HAM-D and YMRS total scores); change in overall illness severity on CGI-BP; time to and rates of hospitalization due to mania or depression.	Mean age 38.5 41% male 51% White 33% Black 14% Hispanic

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Houston, 2009 United States and Puerto Rico	Rapid cycling: 24.5% Psychosis: 2.5% Mean baseline scores: HAM-D: 22.2 YMRS: 20.9 CGI-S: 4.3	446 screened for divalproex response / 202 eligible for DB phase / 202 randomized	84/22/201

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Houston, 2009 United States and Puerto Rico	Olanzapine + divalproex (n=100) vs. placebo + divalproex (n=101): Change from baseline to 6 weeks, mean (SE) 21-item HAM-D -9.37 (0.55) vs. -7.69 (0.54); P=0.022 YMRS -10.15 (0.44) vs. -7.68 (0.44); P<0.001 Median time to partial response 7 vs. 14 days; P<0.001 Median time to response 25 vs. 49 days; P=0.02 Completed study: 57.4% vs. 59%	Clinical chemistry, serum and urine pregnancy tests, lipid panel, vital signs (weight, heart rate, blood pressure).

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Houston, 2009 United States and Puerto Rico	% Olanzapine + divalproex (n=101) vs. % placebo + divalproex (n=101): Sedation 23.8 vs. 4.0; P<0.001 Somnolence 20.8 vs. 5.9; P=0.003 Weight increase of at least 7%: 22 vs. 3; P<0.001 Dry mouth 12.9 vs. 3.0; P=0.017 Increased appetite 12.9 vs. 5.0; P=0.081 Fatigue 9.9 vs. 4.0; P=0.164 Tremor 8.9 vs. 0.0; P=0.003 Headache 5.0 vs. 6.9; P=0.767 Nasopharyngitis 4.0 vs. 6.9; P=0.537 Insomnia 2.0 vs. 5.9; P=0.279 Worsening of symptoms: 1.0 vs. 1.0; P=NS	84 total withdrawals; 12 due to AEs Olanzapine vs. placebo, % of group: Total withdrawals: 42.6% vs. 40.6% Withdrew due to AE: 5.9% vs. 4.0%	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Keck 2009 USA	DB RCT Multicenter - in patient for 2 weeks then released as mania condition improved	Bipolar I disorder, type I, and were experiencing an acute manic or mixed episode (with or without psychotic features) that required hospitalization	Aripiprazole (15–30 mg/day; n=155), placebo (n=165) or lithium (900–1500 mg/day; n=160) for 3 weeks. Aripiprazole- and lithium-treated patients remained on blinded treatment for 9 additional weeks for a total of 12 weeks	Washout 2-14 days
Keck, 2003 United States	RCT Multicenter Hospitalization ≥ 2 weeks	Male and female patients, age ≥ 18 years, diagnosed with bipolar I disorder, manic or mixed episode (DSM-IV), who were experiencing an acute relapse that required hospitalization; YMRS score ≥ 20	Monotherapy Aripiprazole 30 mg daily Placebo 3-week DB	7-day washout

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Keck 2009 USA	Concomitant benzodiazepines were allowed as needed to ameliorate anxiety, agitation or insomnia and Benztropine ≤4 mg/day was permitted to treat extrapyramidal symptoms	Primary = mean change in YMRS Total score from baseline to Week 3 Secondary - CGI-BP, MADRS, PANSS The YMRS and MADRS scale scores were recorded at Day 2, Day 4, Weeks 1, 2, 3, 4, 5, 6, 8, 10, and 12; while the PANSS scores were only assessed at Weeks 3 and 12.	Placebo vs. Lithium vs. Aripiprazole Mean age 39.8 (11.3) vs. 39.6 (10.5) vs. 39.6 (10.6) Male n (%) 86 (52) vs. 84 (52) vs.. 79 (51) Race n(%) White 118 (72) vs. 103 (64) vs. 96 (62) Black 44 (27) vs. 54 (34) vs. 55 (35) Asian 0 vs. 2 (1) vs. 0 American/Alaskan native 3 (2) vs. 0 vs. 2 (1) Other 0 vs. 1 (1) vs. 2 (1)
Keck, 2003 United States	Lorazepam treatment allowed on days 1-4 (≤ 6 mg/day), 5-7 (≤4 mg /day), and 8-10 (≤2 mg/day) Anticholinergic agents limited to 6 mg/day of benztropine (or equivalent) and could not be administered within 12 hours of an efficacy or safety assessment	Primary: YMRS mean change Secondary: Mean change on CGI-BP; discontinuation due to lack of efficacy or entry into open-label aripiprazole treatment; and YMRS response (≥ 50% decrease in mean score) Assessments administered at days 4, 7, 10, 14 and 21	Mean age=40.5 56% female Ethnicity nr

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Keck 2009 USA	Placebo vs. Lithium vs. Aripiprazole n (%) Bipolar manic 105 (64) vs.. 98 (61) vs.. 89 (57) Bipolar mixed 60 (36) vs. 62 (39) vs. 66 (43) Psychotic symptoms present, 41 (25) vs. 39 (24) vs. 31 (20)	715/480/480	At 3 weeks Withdrawals placebo, 53%; lithium, 51%; aripiprazole, 53% LTF placebo, 6%; lithium, 3%; aripiprazole, 10% Analyzed 472 Placebo 163 lithium 155 aripiprazole 154
Keck, 2003 United States	History of rapid cycling=23% Current episode purely manic=67%	NR/NR/262	180/262 (69%) withdrawn Lost to fu nr 248/262 (94.6%) analyzed

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Keck 2009 USA	At week 3 Placebo vs. Lithium vs. Aripiprazole at 3 weeks Change in YMRS at 3 weeks −9.0±0.8 vs. −12.0±0.8 vs. −12.6±0.8 Response (50% or more decrease in YMRS) 34.4 vs. 45.8 vs. 46.8 Remission (YMRS < 12) 28.2 vs. 40 vs. 40.3 CGI-BP Change from preceding phase (mania) 3.1 (0.1) vs 2.9 (0.1) vs 2.5 (0.1)*** Change in MADRS −0.7 (0.6) vs. −1.1 (0.6) vs. −2.1 (0.6) Change in PANSS −4.9 (1.4) vs. −7.0 (1.4) vs.−9.5 (1.4)* *p<0.05; ***p<0.001 vs. placebo Lithium vs. Aripiprazole at 12 weeks Change in YMRS −12.7 ±0.9 vs. −14.5 ±0.9 % Response (50% or more decrease in YMRS) 49.0 vs. 56.5 % Remission (YMRS < 12) 39.4 vs. 49.4 CGI-BP Change from preceding phase (mania) 2.8 (0.1) vs. 2.5 (0.1) Change in MADRS −0.2 (0.8) −0.9 (0.8) Change in PANSS 7.4 (1.6) vs. −10.6 (1.7)	SAS, BARs AIMS and investigator assessment
Keck, 2003 United States	Aripiprazole vs placebo YMRS mean change (points): -8.2 vs -3.4; p=0.002 YMRS response rates (% patients): 40% vs 19%; p≤0.005 CGI overall bipolar disorder mean change (points): -1.0 vs -0.4; p=0.001 Lorazepam treatment: 109/127 (86%) vs 108/127 (85%); p=NS	Investigators evaluated reported events for severity and likely relationship to study medication Extrapyramidal symptoms were evaluated with the Simpson-Angus Rating Scale, Barnes Rating Scale for Drug-Induced Akathisia, and Abnormal Involuntary Movement Scale

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Keck 2009 USA	Placebo vs. Lithium vs. Aripiprazole at 3 weeks, n (%) Akathisia 5 (3.0) vs. 8 (5.0) vs. 17 (11.0) Constipation 10 (6.1) vs. 17 (10.7) vs. 16 (10.4) Headache 37 (22.6) vs. 32 (20.1) vs. 36 (23.4) Nausea 22 (13.4) vs. 37 (23.3) vs. 35 (22.7) Sedation 8 (4.9) vs. 11 (6.9) vs. 18 (11.7) Tremor 8 (4.9) vs. 16 (10.1) vs. 11 (7.1) Lithium vs. Aripiprazole at 12 weeks, n (%) Akathisia 8 (5.0) vs. 23 (14.9) Constipation 20 (12.6) vs. 16 (10.4) Headache 35 (22.0) vs. 36 (23.4) Nausea 38 (23.9) vs. 35 (22.7) Sedation 11 (6.9) vs. 20 (13.0) Tremor 19 (11.9) vs. 12 (7.8)	At 3 weeks Total withdrawals 253 (placebo, 53%; lithium, 51%; aripiprazole, 53%) Due to AEs 56 (placebo group (8%) lithium (13%) and aripiprazole (15%))	
Keck, 2003 United States	Aripiprazole (n=127) vs placebo (n=127) (Statistical analyses not reported; we conducted 2-sided Fisher's exact test using StatsDirect software) Serious adverse events: 4(3.1%) vs 4(3.1%);p=NS Manic reaction: 3(2.4%) vs 0;p=NS Headache: 46(36%) vs 40(31%); p=NS Nausea: 29(23%) vs 13(10%); p<0.05 Dyspepsia: 28(22%) vs 13(10%); p<0.05 Somnolence: 26(20%) vs 6(5%); p<0.001 Agitation: 25(20%) vs 24(19%); p=NS Anxiety: 23(18%) vs 13(10%); p=NS Vomiting: 20(16%) vs 6(5%); p<0.05 Insomnia: 19(15%) vs 11(9%); p=NS Lightheadedness: 18(14%) vs 10(8%); p=NS Constipation: 17(13%) vs 7(6%); p=NS Accidental injury: 15(12%) vs 3(2%); p<0.01 Diarrhea: 15(12%) vs 11(9%); p=NS Akathisia: 14(11%) vs 3(2%); p<0.05	Aripiprazole vs placebo Total withdrawals: 76/130 (58%) vs 104/132 (79%); p<0.001 Withdrawals due to adverse events: 13/132 (10%) vs 14/130 (11%); p=NS	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Keck, 2003 US (21 sites) and Brazil (3 sites)	RCT, DB, Multicenter parallel	Men and women > 18 years of age with a primary DSM-IV diagnosis of bipolar I disorder and a current manic or mixed episode, confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P), were eligible for study participation. Pts were required to have a Mania Rating Scale total > 14, with a score of >2 on at least four items at screening and at baseline (within 12 hours before the first does of double-blind medication). Women of childbearing age were eligible if they had undergone bilateral tubule ligation, hysterectomy, or bilateral total oophorectomy, were 1 year postmenopausal or had tested negative at screening on a serum pregnancy test and had agreed to use investigator-approved contraceptive methods throughout the study.	Monotherapy Ziprasidone 80-160 mg/d Placebo Ziprasidone started at 40 mg bid on day 1, increased to 80mg bid on day 2, and adjusted by a maximum of 40 mg within the range of 80-160mg/d	NR/ 7-day placebo washout

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Keck, 2003 US (21 sites) and Brazil (3 sites)	Lorazepam, temazepam and medications to manage movement disorders allowed; benzodiazepines other than lorazepam or temazepam were permitted with approval of sponsor clinician	Efficacy was asses using the SADS-C (schedule for Affective Disorders and Schizophrenia, Change Version), PANSS, investigator-rated CGI Improvement scale, and Global Assessment of Functioning Scale SADS-C, CGI severity, CGI improvement were administered at screening, baseline (day1), days 2, 4, 7, 14, and 21 (or at study termination, within 12hours of the final dose). PANSS administered on days 1, 7, 14, and 21 (or termination)	Mean age: 38.3 years 54.3% male Ethnicity NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Keck, 2003 US (21 sites) and Brazil (3 sites)	Baseline scores (SD), ziprasidone vs placebo: Mania rating scale score (total): 27.0 (3.8) vs 26.7 (7.0) CGI-S: 4.9 (0.9) vs 4.9 (0.7) PANSS total: 67.0 (15.6) vs 64.4 (15.7) PANSS, positive subscale: 19.5 (6.0) vs 19.0 (5.3) Global Assessment of Functioning Scale: 38.2 (9.7) vs 38.1 (8.8)	274/210/210	Withdrawn=104 (49.5%) Lost to follow-up or withdrew consent=36 (17.1%) Analyzed=197 (93.8%)

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Keck, 2003 US (21 sites) and Brazil (3 sites)	Patients classifying as responders: ziprasidone 50% vs placebo 35%, p<0.05 Mean change in scores from baseline to endpoint, ziprasidone vs placebo Mania rating scale: -12.4 (12.0) vs -7.8 (12.9), p<0.005 CGI-S: -1.3 (1.5) vs -0.9 (1.6), p<0.01 CGI improvement scores at endpoint: 2.9 (1.4) vs 3.5 (1.7), p<0.001 PANSS, positive symptom scores: -4.8 (6.3) vs 2.0 (6.9), p<0.001 Global Assessment of Functioning + 15.3 (18.7) vs +8.3 (18.7), P<0.005	All observed or reported AEs were recorded. Simpson-Angus Rating Scale (SARS) and Barnes Akathisia evaluated at screening, day 1, 7, and 21. Abnormal Involuntary Movement Scale (AIMS), blood pressure, pulse rate, a physical exam, and 12-lead ECG performed at screening, day 1, and study endpoint.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Keck, 2003 US (21 sites) and Brazil (3 sites)	Treatment-emergent AEs: 90.0% vs 77.1% AEs judged to be treatment-related: 70.7% vs 54.3% AEs reported in ≥10% of patients: Somnolence: 37.1% vs 12.9% Headache: 21.4% vs 18.6% Dizziness: 22.1% vs 10.0% Hypertonia: 11.4% vs 2.9% Nausea: 11.4% vs 10.0% Akathisia: 10.7% vs 5.7% Dyspepsia: 10.0% vs 10.0% Insomnia: 7.9% vs 10.0% ziprasidone vs placebo = NS for SARS, AIMS, Barnes Akathisia scale no patient had QTc interval ≥500 msec while taking ziprasidone	all comparisons: ziprasidone vs placebo Total withdrawals: (104/210) 49.5% Withdrawals by drug: (65/140) 46.4% vs (39/70) 55.7% Total withdrawals due to AEs: (12/210) 5.7% Withdrawals due to AEs by drug: (9/140) 6.4% vs (3/70) 4.3%	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Keck, 2006 Keck 2007 US Argentina and Mexico (76 centers)	RCT Multicenter	Inclusion- DSM IV bipolar I age 18 years or more, could provide written consent. Exclusions- Pregnancy or lactation, cognitive disorder, schizophrenia, schizoaffective disorder. Psychotic symptoms explained by other medical condition or substance abuse. Cocaine use Allergy/hypersensitivity to aripiprazole or quinolinones, neuroleptic malignant syndrome, seizure disorder. Clinical trial in past month, electroconvulsive therapy within 2 month	An open-label stabilization phase (aripiprazole monotherapy: 15 or 30 mg/day, 6-18 weeks) then randomized to aripiprazole or placebo for 26 weeks	Stabilization 6-18 weeks
Khanna, 2003 Abstract-only USA and India	RCT Multicenter Hospitalization status unclear	Adults (≥ 18) who provided consent; DSM-IV criteria for bipolar I disorder; voluntary hospitalization with a primary diagnosis of manic or mixed episode; history of at least one prior manic or mixed episode; baseline YMRA score ≥ 20	Risperidone 1-6 mg (mean dose 5.6) Placebo Duration=3 weeks	NR/wash-out unclear

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Keck, 2006 Keck 2007 US Argentina and Mexico (76 centers)	Lorazepam and anticholinergic agents	The primary endpoint was time to relapse for a manic, mixed, or depressive episode (defined by discontinuation caused by lack of efficacy). During double blind phase assessments occurred at day 1, weekly for 4 weeks then every other week until 26 weeks.	Mean age 39.6 years 33% Male 65% white 23% Hispanic 6% black 3% other
Khanna, 2003 Abstract-only USA and India	Lorazepam allowed during washout and for the first 10 treatment days	Primary: Mean change in YMRS total scores Secondary: CGI, PANSS, MADRS, GAS	Mean age=35.1 62% male Ethnicity NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Keck, 2006 Keck 2007 US Argentina and Mexico (76 centers)	Current epitizide Mania 70% Mixed 30%	633 recruited 567 stabilization phase 161 entered RCT	94/ NR/ 161
Khanna, 2003 Abstract-only USA and India	Weight (kg): 54.4 With psychotic features at baseline: 58.8% YMRS Total Score: 37.2 CGI Score: 4 GAS Score: 35.0 MADRS score: 5.1 PANSS total score: 54.2	NR/NR/290	Withdrawn=130 (44.8%)/8 (2.7%) lost to fu/analyzed=unclear

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Keck, 2006 Keck 2007 US Argentina and Mexico (76 centers)	Aripiprazole was superior to placebo in delaying the time to relapse (p = .020). Aripiprazole-treated patients had significantly fewer relapses (25%) than placebo patients (43%; p = .013). Aripiprazole was superior to placebo in delaying the time to manic relapse (p = .01); however, no significant differences were observed in time to depressive relapse (p = .68). Time to relapse in the extension phase (100 weeks) Significantly longer with Aripiprazole Aripiprazole: 7, Placebo=5, Hazard Ratio=0.53; p=0.011, 95% CI=0.32 to 0.87 Time to manic relapse Significantly longer with aripiprazole: p=0.005, hazard ratio, 0.35, 95% CI 0.16 to 0.75 Time to depressive relapse: No difference between Aripiprazole vs placebo. placebo vs aripiprazole Mean (SD)change in YMRS from baseline: 9.4 (1.2) vs 4.9 (1.2), p=0.01 Mean (SD) change in MADRS total score from baseline: 7.9 (1.2) vs 6.2 (1.3), p=0.31 Mean (SD) change in PANSS total score from baseline11.8 (1.6) vs 7.9 (1.7), p=0.10	Patient reported AEs and adverse events were coded using the Coding Symbol for Thesaurus of Adverse Reaction Terms Extrapyramidal symptoms were assessed using the Simpson-Angus Rating Scale and the Abnormal Involuntary Movement Scale and BARS
Khanna, 2003 Abstract-only USA and India	Response (≥ 50% reduction in YMRS total scores): 106 (73%) vs 52 (36%); p<0.001 % Reduction in YMRS Total Score: 28% vs 11%; p<0.001 % GAS improvement: 79% vs 37%; p<0.001 Change in CGI-severity from baseline to week 3 (estimated from graph): -2 vs -1; significance unclear Change in MADRS from baseline to week 3 (estimated from graph): -3 vs -2.2; p<0.01	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Keck, 2006 Keck 2007 US Argentina and Mexico (76 centers)	Placebo vs. aripiprazole % Any AE 69.9 vs. 74.0 Asthenia 8.4 vs. 7.8 Headache 16.9 vs. 7.8 Pain in extremities 1.2 vs. 5.2 Pain in back 6.0 vs. 3.9 Hypertension 3.6 vs. 5.2 Nausea 4.8 vs. 9.1 Anxiety 14.5 vs. 16.9 Insomnia 19.3 vs. 15.6 Depression 14.5 vs. 11.7 Nervousness 6.0 vs. 10.4 Tremor 1.2 vs. 9.1 Agitation 10.8 vs. 7.8 Manic reaction 13.3 vs. 6.5 Somnolence 7.2 vs. 5.2 Depersonalization 9.6 vs. 3.9 Upper respiratory infection 9.6 vs. 9.1 Vaginitis 0 vs. 6.4 Urinary tract infection 3.6 vs. 5.2 Weight gain > 7% 0 vs. 13 AE in the extension phase (100 weeks) Mean change from baseline on Simpson Angus Scale: -0.2 (0.2) vs aripiprazole 0.3 (0.2), p=NS Mean change from baseline in AIMS: 0.05 (0.1) vs 0.3 (0.1), p=NS Mean change from baseline in BARS: -0.2 (0.1) vs 0.02 (0.1), p=NS Mean weight change from baseline: -1.9 (0.8)kg vs 0.4(0.8) kg % of patients with any adverse event: 72.3% vs 77.0% Weight gain: 0% vs 6.5% EPS: 15% vs 22%	Placebo vs. aripiprazole Total 66% vs. 50% due to AES 1% vs. 6%	
Khanna, 2003 Abstract-only USA and India	EPS disorder: 51 (35%) vs 9 (6%); p<0.001 Insomnia: 7 (5%) vs 14 (10%); p=NS Tremor: 15 (10%) vs 1 (1%); p=0.0004 Headache: 9 (6%) vs 4 (3%); p=NS Somnolence: 9 (6%) vs 4 (3%); p=NS Mean body weight changes (kg): +0.1 vs +0.1 QT intervals: no prolongation of QTc intervals (> 500 ms) was observed in either group	Total withdrawals: 57 (39%) vs 73 (51%); p=NS Withdrawals due to adverse events: 5 (3.4%) vs 3 (2.1%); p=NS	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Kwentus; Ortho NCT00309699-2007 U.S., Europe, Asia	DB RCT Multicenter	Men and women aged 18-65 with DSM-IV-diagnosed Bipolar I disorder, most recent episode manic or mixed, currently experiencing an acute manic or mixed episode; history of at least 1 previously documented manic or mixed episode requiring medical treatment within 3 years, and a total score ≥ 20 on YMRS at screening and baseline.	Oral paliperidone extended release, 3 to 12 mg/d Oral quetiapine 400 to 800 mg/day Placebo 3-week DB acute phase, subjects hospitalized for first 7 days; 9-week DB maintenance phase Subjects randomized to active treatment acute phase remained on same treatment in maintenance phase. Subjects initially on placebo crossed over to paliperidone ER (blinded) in maintenance phase.	7 day washout

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Kwentus; Ortho NCT00309699-2007 U.S., Europe, Asia	NR	YMRS, GAF, CGI-BP-S, PANSS, VAS, SF-36 Timing of assessment not fully described. 3-week and 12-week endpoints were analyzed.	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Kwentus; Ortho NCT00309699-2007 U.S., Europe, Asia	NR	NR/NR/493	37/0/491

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Kwentus; Ortho NCT00309699-2007 U.S., Europe, Asia	Paliperidone ER vs quetiapine vs placebo: % of responders: 55.8 vs 49.0 vs 34.6 Mean (SD) change from baseline to 3-week endpoint (LOCF); P-value for paliperidone vs placebo: YMRS total score: -13.2 (8.68) vs -11.7 (9.28) vs -7.4 (10.74); p<0.001 GAF 12.2 (11.17) vs 11.6 (11.96) vs 6.7 (13.56); p<0.001 P-value for paliperidone ER relative to placebo at 3 weeks, results NR: CGI-BP-S: p<0.001 PANSS: p=0.002 Sleep VAS: p<0.001 Paliperidone ER v. quetiapine, mean (SD) change from baseline to 12-week endpoint (LOCF): YMRS total score -15.2 (10.26) vs -13.5 (11.02); p=NS	Clinical labs, 12-lead ECGs, vital sign measurements, blood pressure, pulse, physical exam, including height, weight, and waist circumference; EPS monitored using AIMS, BARS, SAS; MADRS and SSI; depression and suicidality monitored using MADRS and SSI.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Kwentus; Ortho NCT00309699-2007 U.S., Europe, Asia	1 suicide in quetiapine during maintenance phase; 1 suicide in placebo/paliperidone ER group 5 days after withdrawal from study (timing of withdrawal NR). Depression: 5 (5%) in placebo/paliperidone ER and 14 (7%) in paliperidone ER; 0 in quetiapine Paliperidone ER vs quetiapine vs placebo: % of subjects with abnormally high heart rate: 20 vs 19 vs 10 % of subjects with ≥7% weight increase at end of maintenance phase: 8 v 17 v 6 EPS: akathisia, hypertonia, drooling, extrapyramidal disorder, and muscle spasms more frequent in paliperidone ER than placebo, results NR. % of subjects receiving anticholinergic medications during acute treatment phase: 17 vs 7 vs 5. % of subjects with prolactin-related AEs during combined acute and maintenance phases: 5 vs 3 vs 2. Mean (SD) increases in prolactin (ng/mL) at 3-week endpoint: Paliperidone ER: 24.61 (23.98) in males; 89.77 (81.47) in females. Placebo: -1.03 (14.08) in males; 7.15 (31.82) in females Quetiapine: No increase in mean prolactin.	Total withdrawals NR; 37 withdrawals due to AEs	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Macfadden, 2009 United States and India	RCT, DB Multicenter (32)	Inclusion: Patients aged 18-70 with DSM-IV diagnosed bipolar disorder type I or II (only type I analyzed in this report), with ≥4 episodes requiring psychiatric intervention in the past 12 months, and in any phase of bipolar illness (manic, hypomanic, depressed, mixed, or euthymic) at study entry. Usual treatment and risperidone LA injectable dosage stable for at least 4 weeks prior to randomization. Exclusion: DSM-IV diagnosed substance dependence; risk of injury to self or others; treatment with carbamazepine, oxcarbazepine, fluoxetine, paroxetine, or clozapine within one month of baseline; significant medical illness; or clinically significant abnormal lab or physical exam findings.	52-week DB relapse prevention phase: All patients that stabilized open-label phase (usual treatment plus risperidone LA injectable) were randomized to receive placebo injection or risperidone LA injectable to assess relapse. Risperidone LA injectable starting at final dosage of open-label phase (25 to 50 mg every 2 weeks). Controls received placebo injection every 2 weeks.	16-week open label stabilization phase of risperidone LA injectable (25 to 50 mg every 2 weeks) plus patient's usual treatment.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Macfadden, 2009 United States and India	Open-label phase: allowed oral antipsychotics that were part of patient's usual treatment for 3 weeks after first risperidone LA injection. Patients not taking oral antipsychotics received oral risperidone for the first 3 weeks. Double-blind phase: lorazepam up to 3 doses per week, 10 doses per month. Supplemental oral risperidone up to 3 consecutive days for worsening of symptoms. Usual treatment: any combination of antidepressants, mood stabilizers, or anxiolytics.	Efficacy: YMRS, MADRS, CGI-Bipolar-S, CGI-Bipolar-C at weeks 0, 4, 8, 12, 14, 16, 22, 28, 28, 34, 42, 48, 54, 60, and 68 or endpoint. Relapse was determined by an independent monitoring board, based on worsening of symptoms (YMRS>15 or MADRS>15; or CGI-BP-S≥4 or CGI-BP-C≥6 or GAF decrease by >10) or hospitalization for symptom worsening of YMRS or MADRS score>15, CGI-BP-S score ≥4 or CGI-BP-C≥6 or GAF>10 from baseline. Hospitalization for worsening of manic or depressive episodes with significant suicidal ideation INTERSEPT scale for suicidal thinking revised score >7	Mean age 38.9 male 71.8 % White 9.7 % Hispanic 0.8 % Black 6.5 % Other (east India) 83.1 %

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Macfadden, 2009 United States and India	Mean age onset 26.5 Mean N episodes in past 12 months: 5.2 Most recent episode: % Depressed 29.8 % Manic 54.8 % Mixed 6.5 % Hypomanic 8.9 Weeks since most recent episode, mean7.1	271 screened / 240 enrolled in OL phase / 124 randomized in DB phase	60/9/124

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Macfadden, 2009 United States and India	Risperidone LA injectable (N=65) vs. placebo (N=59): Completed study: 60.0% vs. 42.4% Time to relapse significantly delayed with adjunctive risperidone long-acting injection compared with adjunctive placebo (p=0.010) Relapse rate: 23.1% vs. 45.8% RR of relapse was 2.3-fold higher with placebo compared to adjunctive risperidone LA injectable in Cox regression; P=0.011. Mean (SD) change from start of DB relapse prevention phase to endpoint: YMRS 1.7 (7.2) vs. 7.6 (13.5); P≤0.05 MADRS 1.7 (7.0) vs. 2.5 (8.8); P=ns CGI-bipolar-S overall≥4: 0.3 (1.3) vs. 1.1 (1.9); P≤0.05 CGI-bipolar-S mania 0.2 (1.0) vs. 0.9 (1.6); P≤0.05 CGI-bipolar-S depression -0.2 (1.0) vs. 0.1 (1.4); P=ns CGI-bipolar-C at endpoint: Overall 4.1 (1.2) vs. 4.6 (1.3); P≤0.05 Mania 4.0 (1.0) vs. 4.5 (1.2); P≤0.05 Depression 4.0 (0.9) vs. 4.1 (0.9); P=ns	Clinical labs (hematology, biochemistry, and urinalysis), ECGs - at screening and week 68 or endpoint. Vital signs - each visit. Physical exam - at screening, week 16, and endpoint. ISST and movement disorder scale ratings (SAS, BAS, AIMS) - at weeks 0, 16, 28, 42, 54, and 68 or endpoint.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Macfadden, 2009 United States and India	Risperidone LA injectable vs. placebo, %: Tremor 24.6 vs. 10.2 Insomnia 20.0 vs. 18.6 Muscle rigidity 12.3 vs. 5.1 Weight increased 6.2 vs. 1.7 Hypokinesia 7.7 vs. 0 Pyrexia 4.6 vs. 8.5 Akathisia 4.6 vs. 6.8 Upper respiratory infection 6.2 vs. 1.7 Sedation 6.2 vs. 0 Mania 4.6 vs. 13.6 Dizziness 4.6 vs. 6.8 Suicidal ideation 1.5 vs. 5.1 Headache 0 vs. 8.5 Depression 0 vs. 8.5 Fatigue 0 vs. 5.1 Nausea 0 vs. 5.1 Injury 0 vs. 5.1	60 total withdrawals; 4 due to adverse events Risperidone LA injectable vs. placebo, % of group: Total withdrawals: 40.0% vs. 57.6% Withdrew due to AE: 4.6% v. 1.7%	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
McElroy, 2010 United States, EU member states, Turkey, Central and South America, South Africa, Australia EMBOLDEN II	DB RCT Multicenter (83 centers)	Inclusion: Patients aged 18 years or older, with a documented clinical diagnosis of bipolar I or II disorder, most recent episode depressed, as defined by DSM-IV, with or without a rapid-cycling course (≥ 4 episodes to ≤ 8 episodes per year), were eligible for inclusion in the study. Additional enrollment criteria included a HAM-D score ≥ 20, an HAM-D item 1 (depressed mood) score ≥ 2, and a YMRS score ≤ 12. Exclusion: Patients with a DSM-IV diagnosis of an Axis I disorder other than bipolar disorder that was the primary focus of treatment within the 6 months prior to screening; Patients with a previously known lack of response to quetiapine or paroxetine therapy; a diagnosis of current episode of depression exceeding 12 months or less than 4 weeks in duration from enrollment, HAM-D item 3 (suicide) score ≥ 3, more than 8 mood episodes 12 months prior to enrollment, substance dependence diagnosis (DSM-IV) or substance use (with the exception of nicotine) within 12 months prior to screening, clinically significant comorbid diseases, and the use of drugs that induce or inhibit the hepatic metabolizing cytochrome P450 3A4 enzymes in the 14 days prior to enrollment; Female patients who were pregnant, lactating, or of childbearing potential and not using a reliable method of contraception	Quetiapine 300 mg/day vs quetiapine 600 mg/day vs paroxetine 20 mg/day vs placebo 8 weeks	Washout phase of 5 to 28 days

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
McElroy, 2010 United States, EU member states, Turkey, Central and South America, South Africa, Australia EMBOLDEN II	Patients were allowed to continue taking previous medications for nonpsychiatric medical illnesses throughout the study. Concomitant treatment with other psychoactive drugs was prohibited except for lorazepam (1–3 mg/d), zolpidem tartrate (≤ 10 mg/d), zaleplon (≤ 20 mg/d), zopiclone (≤ 7.5 mg/d), and chloral hydrate (≤ 1 g/d), which were permitted during the first 3 weeks of the study. Anticholinergics were permitted to treat extrapyramidal symptoms (EPS), but prophylactic use was prohibited.	MADRS, assessed at baseline, week 1, 2, 4, 6, 8; CGI severity of illness and change; HAS; Sheehan Disability Scale; Quality of Life Enjoyment and Satisfaction Questionnaire	Mean age: 38.6 years 37.4% male Ethnicity: NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
McElroy, 2010 United States, EU member states, Turkey, Central and South America, South Africa, Australia EMBOLDEN II	Quetiapine 300 mg/day vs quetiapine 600 mg/day vs paroxetine vs placebo Bipolar I disorder: 64.6% vs 64.7% vs 62.7% vs 62.8% Bipolar II disorder: 35.4% vs 35.3% vs 37.3% vs 37.2% Mean MADRS: 27.1 vs 26.5 vs 27.3 vs 27.2 Mean HAM-D: 24.2 vs 24.2 vs 24.1 vs 24.2 Mean HAS: 18.6 vs 18.5 vs 18.8 vs 18.6 Mean YMRS: 5.5 vs 5.9 vs 5.5 vs 5.9	1076/NR/740	269/80/700

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
McElroy, 2010 United States, EU member states, Turkey, Central and South America, South Africa, Australia EMBOLDEN II	Quetiapine 300 mg/day vs quetiapine 600 mg/day vs paroxetine vs placebo *P* value is versus placebo Mean change in MADRS: -16.19; *P* <0.001 vs -16.31; *P* <0.001 vs -13.76; *P* =0.313 vs -12.6 Mean change in MADRS item 10: -0.71; *P* =0.035 vs -0.76; *P* =0.010 vs -0.55; *P* =0.759 vs -0.52 Mean change in HAM-D: -14.68; *P* <0.001 vs -15.09; *P* <0.001 vs -12.53; *P* =0.24 vs -11.42 Mean change in HAM-D item 1: -1.66; *P* <0.01 vs -1.67; *P* <0.01 vs -1.51; *P* =0.196 vs -1.33 Mean change in HAS: -10.61; *P* <0.001 vs -10.19; *P* <0.001 vs -9.15; *P* =0.033 vs -7.32 Mean change in CGI-S: -1.67; *P* =0.012 vs -1.65; *P* =0.018 vs -1.44; *P* =0.478 vs -1.33 Mean change in Quality of Life Enjoyment and Satisfaction Questionnaire: 8.75; *P*= 0.197 vs 8.96; *P* =0.139 vs 7.96; *P* =0.604 vs 7.28 Mean change in Sheehan Disability Scale: -6.97; *P* =0.291 vs -6.66; *P* =0.471 vs -6.04; *P* =0.969 vs -6	The incidence, severity, and withdrawals attributed to adverse events (AEs) were recorded at each visit; Treatment-emergent mania or hypomania (YMRS score ≥ 16 on 2 consecutive visits or at final assessment or treatment-emergent mania/hypomania reported as an AE) and the proportion of patients with treatment-emergent suicidal ideation (HDRS item 3 [suicide] score ≥ 3 or an AE of suicidality, suicidal ideation, suicide attempts, or suicide completion); Vital signs and laboratory test results, weight and BMI, ECG, and physical examination results. EPS (SAR-S and BARS and AIMS); Sexual Functioning Questionnaire.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
McElroy, 2010 United States, EU member states, Turkey, Central and South America, South Africa, Australia EMBOLDEN II	Quetiapine 300 mg/day vs quetiapine 600 mg/day vs paroxetine vs placebo Any AEs: 65.8% vs 70.1% vs 69.4% vs 62.9% Serious AEs: 0.4% vs 3.7% vs 7.4% vs 3.2% Dry mouth: 21.8% vs 25.8% vs 9.9% vs 5.6% Somnolence: 18.9% vs 17.6% vs 5.8% vs 8.1% Sedation: 12.8% vs 16% vs 8.3% vs 4.8% Dizziness: 11.5% vs 13.9% vs 6.6% vs 5.6% Headache: 9.9% vs 9.8% vs 15.7% vs 12.9% Fatigue: 6.6% vs 7.8% vs 3.3% vs 3.2% Constipation: 5.8% vs 9% vs 5% vs 1.6% Nausea: 5.8% vs 9% vs 12.4% vs 5.6% Dyspepsia: 3.3% vs 5.7% vs 1.7% vs 2.4% Increased appetite: 3.3% vs 5.3% vs 2.5% vs 2.4% Insomnia: 2.1% vs 2% vs 13.2% vs 10.5% Diarrhea: 1.6% vs 2.9% vs 6.6% vs 4% Decreased appetite: 0.8% vs 0.8% vs 5% vs 0 Anxiety: 0.4% vs 2.5% vs 5% vs 5.6% Treatment-emergent mania or hypomania: 2.1% vs 4.1% vs 10.7% vs 8.9% Treatment-emergent suicidal ideation: 2.9% vs 2% vs 3.3% vs 4%) EPS-related AEs: 8.2% vs 9.8% vs 4.1% vs 2.4% Mean change in BARS: -0.1 vs -0.1 vs 0 vs 0 Worsened SAR-S: 9.3% vs 8.6% vs 12% vs 14.3% Weight change (SE): 1.1 (0.21) vs 1.7 (0.23) vs -0.3 (0.29) vs 0.5 (0.27) kg Prolactin change (SE): -0.15 (1.12) vs -1.43 (0.78) vs -0.06 (0.99) vs -1.44 (1.08) µg/L	Quetiapine 300 mg/day vs quetiapine 600 mg/day vs paroxetine vs placebo Total withdrawals: 85 vs 88 vs 46 vs 50 Withdrawals due to AEs: 21 vs 30 vs 15 vs 10	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
McIntyre 2005 Brecher, 2003 (poster) United States	RCT, DB Multicenter Parallel	Male and female (≥ 18 years of age) with a DSM-IV diagnosis of bipolar I disorder and at least one prior manic or mixed episode; hospitalized with a manic episode (eligible for discharge after Day 7); YMRS score ≥ 20, including score ≥ on 2 of the core YMRS items of Irritability, Speech, Content, and Disruptive/Aggressive Behavior; CGI-BP Severity of Illness score ≥ 4	Quetiapine (QTP): 100, 200, 300, and 400 mg/d on Days 1, 2, 3, and 4, respectively; 200-600 mg/d on Day 5; 200-800 mg/day on Days 6-84 Haloperidol (HPL): 2 mg/day on Days 1-2, 3 mg/day on Day 3; 4 mg/day on Day 4; 2-6 mg/day on Day 5; 2-8 mg/day on Days 6-84 Placebo (PBO) Duration: up to 12 weeks	NR/NR
McIntyre 2009 Olympia Clinical Trial Program United States, India, Russia, Ukraine, Korea, Bulgaria, Philippines, Romania, Turkey, Malaysia	RCT, DB Multicenter (55)	Inclusion: Patients ≥18 years old with DSM-IV diagnosed bipolar I disorder; with current manic or mixed bipolar I episode that began ≤3 months before screening visit; YMRS total score ≥20; history of >1 previous episode. Exclusion: women who were or could become pregnant; psychotic disorder; rapid-cycling bipolar disorder during past year; DSM-IV substance dependence; positive screen for psychomotor stimulants; seizure disorder; HIV; unstable medical condition or lab abnormality; previously participated in asenapine trial; clozapine within 12 weeks; investigational drug within 30 days of baseline.	Asenapine sublingual, flexible dose (5 or 10 mg BID; mean 18.2 mg/day), N=194 Oral olanzapine (5-20 mg QD, mean 15.8 mg/day), N=191. Placebo, N=104. 3 weeks	Single-blind placebo run-in up to 7 days

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
McIntyre 2005 Brecher, 2003 (poster) United States	Previously prescribed medications for stable medical conditions Zolpidem tartrate, chloral hydrate, zopiclone, or zaleplon for insomnia Lorazepam (for agitation) titrated down from 6 mg/d at screening to 1 mg/d by Day 11 and not permitted after Day 14	Primary: Change from baseline in YMRS score at Day 21 Secondary (assessed at Day 21 and Day 84): Change from baseline in YMRS score; YMRS response rate (percent of patient ≥ 50% improved); YMRS remission rate (percent of patients with YMRS score ≤ 12); % of patients maintaining YMRS response of remission; CGI and CGI-BP response rate (% of patients rated as "much" or "very much" improved from baseline on Global Improvement scale); Change from baseline in CGI and CGI-BP severity of illness scores, PANSS scores; MADRS score, GAS score	Mean age=42.9 63.2% female Ethnicity NR
McIntyre 2009 Olympia Clinical Trial Program United States, India, Russia, Ukraine, Korea, Bulgaria, Philippines, Romania, Turkey, Malaysia	EPS medications, benzodiazepines, and non-benzodiazepine sedative-hypnotics allowed only for first 7 days. Allowed hormonal birth control, anti-hypertensives, diuretics, and oral hypoglycemics. Aspirin and NSAIDS as needed.	YMRS and CGI-BP assessed at screening, baseline, and treatment days 2, 4, 7, 14, and 21 or endpoint. MADRS assessed at days 7 and 21 or endpoint. Response rate defined as ≥ 50% decrease in YMRS total score; percentage of remitters (YMRS total score ≤12 at endpoint).	Mean age 39.4 57.4% male White 60.5% Black 16.6% Asian 18.0% Other 4.9%

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
McIntyre 2005 Brecher, 2003 (poster) United States	Mean weight (kg): 70.7 Mean BMI (kg/m2): 25.6 Mean YMRS total score: 33.1 Manic, moderate: 28.8% Manic, severe: Without psychotic features: 29.4% With psychotic features: 41.8%	NR/NR/302 (QTP n=102; PBO n=101; HPL n=99)	Withdrawn=50.5%/Lost to fu=1.6%/analyzed=299 (QTP=101; PBO=100; HPL=98)
McIntyre 2009 Olympia Clinical Trial Program United States, India, Russia, Ukraine, Korea, Bulgaria, Philippines, Romania, Turkey, Malaysia	Type of episode: Mania 69.3% Mixed 30.7%	654 screened / NR eligible / 489 enrolled	151/9/488

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
McIntyre 2005 Brecher, 2003 (poster) United States	Mean change in YMRS (QTP vs PBO) Day 21: -12.3 vs -8.3, p=0.01 Day 84: -17.5 vs -9.5, p<0.001 Response/remission for QTP vs PBO (% patients) (estimated from graph) Day 21 YMRS response: 41% vs 35%, ns YMRS remission: 27% vs 24%, ns CGI-BP response: 42% vs 32%, ns Day 84 YMRS response: 59% vs 39%, p<0.001 YMRS remission: 60% vs 39%, p<0.001 CGI-BP response: 50% vs 30%, p<0.001 PANSS Total Score: QTP>PBO in mean reductions at Days 21 and 84 (p<0.05) (data nr) MADRS mean reductions: QTP > PBO at Day 21 (p=0.005) and Day 84 (p=0.008) GAS mean increases: QTP > PBO at Days 21 (p<0.023) and 84 (p<0.001)	NR
McIntyre 2009 Olympia Clinical Trial Program United States, India, Russia, Ukraine, Korea, Bulgaria, Philippines, Romania, Turkey, Malaysia	Asenapine vs. olanzapine vs. placebo: Change in total score from baseline to day 21, mean ± SD; P-value vs. placebo: YMRS: -10.8 ± 0.8 vs. -12.6 ± 0.8 vs. -5.5 ± 10; both treatments P<0.0001. CGI-BP: -1.2 ± 0.1; P ≤0.01 vs. -1.4 ± 0.1; P ≤0.0001 vs. -0.7 ± 0.13 MADRS: -3.2 ± 0.5; P=ns vs. -4.2 ± 0.5; P ≤ 0.01 vs. -1.8 ± 0.7 Response rate: 42.3% vs. 50% vs. 25.2% Proportion of remitters: 40.2% vs. 39.4% vs. 22.3%	Observed by investigator or spontaneously reported by patient; vital signs assessed at each visit; ECG, urine samples, and body weight assessed at screening and day 21. Metabolic indices at baseline and study endpoint. EPS assessed using BARS, AIMS, SAS.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
McIntyre 2005 Brecher, 2003 (poster) United States	Treatment-emergent depression (MADRS score of ≥ 18 with an increase from baseline of ≥ 4 at any 2 consecutive assessments or at last observation): QTP=2.9% vs PBO=8.9%; HPL=8.1% Mean change in weight (day 84) (observed cases) (kg): QTP=+2.1 vs PBO=-0.1, HPL=+0.2, p=nr QTP (n=102) vs PBO (n=101) vs HPL (n=99), p-value for QTP vs PBO, p-value for QTP vs HPL Insomnia: 20 (19.6%) vs 20 (19.8%) vs 14 (14.1%), p=ns, p=ns Somnolence: 13 (12.7%) vs 5 (5%) vs 9 (9.1%), p=ns, p=ns EPS-related: 13 (12.7%) vs 16 (15.8%) vs 59 (59.6%), p=ns, p<0.0001 Akathisia: 6 (5.9%) vs 6 (5.9%) vs 33 (33.3%), p=ns, p<0.0001 Tremor: 8 (7.8%) vs 6 (5.9%) vs 30 (30.3%), p=ns, p<0.0001 Agitation: 8 (7.8%) vs 9 (8.9%) vs 8 (8.1%), p=ns, p=ns Dry mouth: 7 (6.9%) vs 4 (4%) vs 4 (4%), p=ns, p=ns Postural hypotension: 6 (5.9%) vs 1 (1%) vs 2 (2%); p=ns, p=ns Headache: 5 (4.9%) vs 4 (4%) vs 8 (8.1%), p=ns, p=ns	QTP vs PBO vs HPL, p-value for QTP vs PBO, p-value for QTP vs HPL Total withdrawals: 47 (46.1%) vs 59 (58.4%) vs 45 (45.5%), p=ns, p=ns Withdrawals due to adverse events/concurrent illness: 5 (4.9%) vs 6 (5.9%) vs 10 (10.1%), p=ns, p=ns	
McIntyre 2009 Olympia Clinical Trial Program United States, India, Russia, Ukraine, Korea, Bulgaria, Philippines, Romania, Turkey, Malaysia	Asenapine (N=194) vs placebo (N=105) vs olanzapine (N=189), % of group: Mania 3.1 vs 2.9 vs 1.1 Agitation 1 .0 vs 0 vs 1.1 Sedation 18.6 vs 4.8 vs 18.5 Dizziness 11.9 vs 3.8 vs 8.5 Somnolence 8.8 vs 1.9 vs 7.4 Fatigue 6.2 vs 1.0 vs 4.8 Oral hypoesthesia 5.2 vs 1.0 vs 1.1 Dry mouth 4.1 vs 1.0 vs 14.3 Weight increase 3.1 vs 1.0 vs 6.9 Any EPS related AE 7.2 vs 2.9 vs 7.9 AIMS score ≥2: 1.1 vs 1.0 vs 1.6 BARS global score ≥2: 7.4 vs 5.2 vs 7.9 SAS mean total score >0.3: 5.5 vs 2.0 vs 2.8 Mean weight change, kg: 1.6 vs 0.3 vs 1.9 Abnormal ECG in 1% vs 2% vs 0%	151 withdrawals 35 due to AEs	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
McIntyre, 2009 Bulgaria, India, Malaysia, Philippines, Republic of Korea, Romania, Russia, Turkey, Ukraine, and the United States	DB extension trial Multicenter	Patients who completed one of the 3-week trials (Ares 7501004, Ares 7501005) were eligible for the extension study if they wished to participate, if they had no major protocol violations, and if the investigator judged that continued treatment could be of clinical benefit; those who did not complete a 3-week trial were excluded from the extension study.	Flexible dose Sublingual asenapine (5-10 mg) BID vs oral olanzapine (5-20mg) QD extended for 9 weeks Note: Patients who had received placebo in the 3-week trials were blindly switched to asenapine (labelled as placebo/asenapine group)	No washout. Continued immediately from the end of the 3-weeks trials

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
McIntyre, 2009 Bulgaria, India, Malaysia, Philippines, Republic of Korea, Romania, Russia, Turkey, Ukraine, and the United States	Lorazepam up to 4 mg/day for agitation, aspirin or nonsteroidal anti-inflammatory drugs for pain, and antiparkinsonian medications for EPS; hypnotics/ benzodiazepines (zolpidem 10 mg/day, zaleplon 20 mg/day, or temazepam up to 30 mg/day for no more than 3 nights per week) were permitted for insomnia.	Change in YMRS total score (administered weeks 1, 3, 6, and 9); percentage of YMRS responders (defined as ≥50% decrease from baseline in YMRS total score) and remitters (YMRS total score ≤ 12) at study endpoint; CGI; MADRS; PANSS; Short Form 36 (SF-36) at end of study	Placebo/Asenapine vs Asenapine vs Olanzapine Mean age (SD): 40 (13.1) vs 39.1 (13.0) vs 39.6 (11.9) years Male: 48% vs 54% vs 59% White: 59 (63) vs 108 (60) vs 131 (57) Black: 19 (20) vs 20 (11) vs 27 (12) Asian or other: 16 (17) vs 53 (29) vs 71 (31)

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
McIntyre, 2009 Bulgaria, India, Malaysia, Philippines, Republic of Korea, Romania, Russia, Turkey, Ukraine, and the United States	Asenapine vs Olanzapine Mean YMRS total score (SD): 29.0 (6.1) vs 28.8 (5.9) Mean MADRS (SD): 9.7 (7.3) vs 10.3 (7.1)	680/NR/504	196/42/397 (see comments)

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
McIntyre, 2009 Bulgaria, India, Malaysia, Philippines, Republic of Korea, Romania, Russia, Turkey, Ukraine, and the United States	asenapine vs olanzapine Mean change YMRS total score (SD): -20.1 (10.7) vs -21.3 (9.6) Response rate: 77% vs 82% Remission rate: 75% vs 79% Mean change MADRS (SE): -3.6 (0.69) vs -2.4 (0.61); *P* =NS	Adverse events reported by the patient or observed by the investigator were recorded; changes from baseline in laboratory variables and metabolic chemistries, including cholesterol, liver enzymes, and glucose levels; electrocardiograms; vital signs; and physical examination; weight gain (≥ 7% increase from baseline) or loss (≥ 7% decrease from baseline); BMI; extrapyramidal symptoms: SAR-S, BARS, AIMS

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
McIntyre, 2009 Bulgaria, India, Malaysia, Philippines, Republic of Korea, Romania, Russia, Turkey, Ukraine, and the United States	Placebo/Asenapine vs Asenapine vs Olanzapine Mean change in SAR-S (SD): -0.2 (1.07) vs 0.1 (1.3) vs -0.1 (1.74) Mean change in BARS (SD): -0.4 (1.55) vs 0.1 (1.3) vs -0.1 (1.13) Mean change in AIMS (SD): 0 (0.33) vs 0 (0.31) vs 0 (0.23) n (%) All AEs: 72 (77) vs 139 (77) vs 178 (78) All serious AEs: 13 (14) vs 22 (12) vs 22 (10) Sedation: 8 (9) vs 26 (14) vs 40 (18) Dizziness: 7 (7) vs 24 (13) vs 15 (7) Insomnia: 8 (9) vs 23 (13) vs 23 (10) Headache: 13 (14) vs 21 (12) vs 34 (15) Somnolence: 13 (14) vs 21 (12) vs 33 (14) Nausea: 11 (12) vs 15 (8) vs 7 (3) Weight gain: 3 (3) vs 14 (8) vs 33 (14) Constipation: 10 (11) vs 10 (6) vs 10 (4) Dry mouth: 3 (3) vs 7 (4) vs 25 (11) Akathisia: 4 (4) vs 13 (7) vs 20 (9) Parkinsonism: 3 (3) vs 10 (6) vs 4 (2) Dystonia: 3 (3) vs 6 (3) vs 5 (2) Bradykinesia: 0 vs 4 (2) vs 3 (1)	Total Withdrawals: 196 Withdrawals due to AEs: 64	Patients who had received placebo in the 3-week trials were blindly switched to asenapine and these patients were included in the safety analyses only.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Meehan, 2001 United States and Romania	RCT, DB Multicenter	Male or female subjects ≥18 years who had DSM-IV-diagnosed bipolar disorder, manic or mixed. Confirmation of the diagnosis occurred through administration of the Structured Clinical Interview for DSM-III-R (SCID). Pts were required to (1) be deemed by site physicians to have agitation severe enough to be appropriate candidates for receiving injections; (2) have a minimum total score=14 on the 5 items comprising the (PANSS)-Excited Component (PANSS-EC); and (3) have at least one individual item score of ≥4, with the 1 - 7 scoring system, immediately before randomization.	Olanzapine - first 2 of 3 possible injections were 10mg/injection; last injection was 5mg Lorazepam - first of 3 possible injections were 2 mg/injections; last injection was 1 mg Placebo - first 2 of 3 possible injections were placebo; 3rd injection was 10 mg olanzapine Screening period + 24 hour treatment period Each patient received first injection; a 2nd and 3rd injection was up to the investigator	None

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Meehan, 2001 United States and Romania	Lithium and valproate allowed concomitantly (46.5%, 39.2%, 52.9% of olan, lzp, pla patients respectively); prophylactic use of anticholinergic medications prohibited, but benztropine, biperiden, or procyclidine were allowed as required for control of EPS.	Primary efficacy: PANSS - EC Secondary outcomes: the 14-item ABS (Agitated Behavior Scale); the single-item 9-point ACES (Agitation-Calmness Evaluation Scale) developed by Eli Lilly; the BPRS, the CGI-S, PANSS-derived PBRS, YMRS.	Mean age: 40.0 yrs 53.2% male 72.6% white 15.9% black 11.5% other

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Meehan, 2001 United States and Romania	Current manic, mixed, with psychotic features: 52.3% of patients Rapid cycling: 52.2%	NR/NR/201	7 / NR / 199 patients on most tests (171 on YMRS and 174 on PANSS-derived BPRS positive)

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Meehan, 2001 United States and Romania	Olanzapine vs lorazepam vs placebo % of patients who completed study: 99.0% vs 94.1% vs 90.0% (p=0.034) % of patients who needed a second and a third injection: 26.3% vs 52.9% vs 52.9% (p=0.002 for olan vs lzp and p<0.001 vs pla) Mean change (SD) in efficacy measures (LOCF): PANSS-EC, at 2 hours: -9.60(4.74) vs -6.75(2.97) vs -4.84 (4.66) (p=0.001 olz vs lzp; p<0.001 for olz vs pla) at 24 hours: -5.78 (4.72) vs -5.65 (5.20) vs -3.94 (4.32) (p=NS olz vs lzp; p=0.025 for olz vs pla) at 2 hours, mean change significant for olz vs lzp in 3/4 scales: ABS, ACES, PANSS-derived BPRS total at 2 hours, mean change significant for olz vs pla in 4/4 scales: ABS, ACES, PANSS-derived BPRS total, and PANSS-derived BPRS positive at 24 hours, mean change significant for olz vs lzp in 0/6 scales : at 24 hours, mean change significant for olz vs pla in 4/6 scales: ABS, ACES, PANSS-derived BPRS total, and PANSS-derived BPRS positive	EPS assessed by the Simpson-Angus Extrapyramidal Effects Scale (S-A) and the Barnes Akathisia Global (Barnes) score AEs were solicited from the patient and ECG measurements were made.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Meehan, 2001 United States and Romania	Olanzapine vs lorazepam vs placebo % of patients experiencing ≥1 treatment-emergent AE 34.3% (34 patients) vs 51.0% (26 patients) vs 25.5% (13 patients) olz vs lzp, p=NS; olz vs pla, p=NS Somnolence: 13.1% vs 9.8% vs 5.9% Dizziness: 13.7% vs 9.1% vs 2.0% Nausea: 1.0% vs 7.8% vs 0% (significant among treatment groups, p=0.031) Vomiting: 0% vs 5.9% vs 2% (significant among treatment groups, p=0.040) No other treatment-emergent AE occurred in ≥10% of any group Other AEs in olanzapine group: dry mouth (3.0%), abnormal gait (2.0%), hallucinations (2.0%), pharyngitis (2.0%), and tremor (2.0%). None were significant. 12 patients total received anticholinergic medication during the 24h intramuscular period: 8 olan patients, 1 lorazepam patient, and 3 placebo patients Two placebo patients who had received their crossover 3rd injection of olanzapine withdrew for agitation and hostility	2 withdrawals; 2 withdrawals (both in placebo, due to agitation and hostility)	Patients in placebo used Lithium more than in other two groups: pla=31.4% vs lzp=15.7% vs olan 14.1% (p=0.037)

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Morozova; Ortho NCT00132678-2007 Austria, India, Malaysia, Poland, Russia, Slovakia, Spain, Taiwan, Ukraine, U.S.A	DB RCT Multicenter	Male or female subjects aged 18-65 with Bipolar I disorder, currently experiencing a manic or mixed episode (YMRS≥20) or were between mood episodes (stable; CGI-S ≤3, mild); did not meet DSM-IV-TR criteria for a depressive episode; and in good physical health. 4 phases are described (Periods II-V). Subjects with an acute episode or subjects stable on an antipsychotic other than risperidone were eligible to enter 3 weeks of open-label oral risperidone (Period II). Those who responded during Period II and subjects stable on risperidone at screening were eligible for a 6-month open-label stabilization period of risperidone long-acting injectable (Period III). To enter the double-blind phase (Period IV), subjects were required to have maintained a treatment response during Period III, and had a stable dose of risperidone long-acting injectable for the last 8 weeks of Period III. After at least 1 visit during Period IV, subjects were eligible for an 8-week open-label extension (Period V) of risperidone long-acting injectable.	Period II: oral risperidone tablets, 1 to 6 mg/day, for 3 weeks. Periods III, IV, and V: risperidone long-acting injectable, administered intramuscularly every 2 weeks, in 4 strengths: 12.5, 25, 37.5, or 50 mg. Titration was allowed during the first 18 weeks of Period III (6-month stabilization). A dose change was not allowed during the last 8 weeks of treatment. Period IV, DB phase: subjects randomized to risperidone long-acting injectable continued the dose they received during the last 8 weeks of Period III; dose titration was not allowed. Subjects assigned to placebo received placebo injections administered i.m. every 2 weeks. Period V: Subjects entering the open-label extension from the DB treatment received 25 mg of risperidone long-acting injectable on Day 1, with dose-titration allowed at 2-week intervals.	None

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Morozova; Ortho NCT00132678-2007 Austria, India, Malaysia, Poland, Russia, Slovakia, Spain, Taiwan, Ukraine, U.S.A	NR	Primary outcome: time to relapse of a mood episode. YMRS, MADRS, CGI-S scale - used throughout the study. Personal Social Performance Scale and SF-36 - used throughout study except during open-label phase RUQ - during DB phase Intensive Resource Use Questionnaire - during open-label extension	Mean age 39.2 51% male 80% Caucasian

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Morozova; Ortho NCT00132678-2007 Austria, India, Malaysia, Poland, Russia, Slovakia, Spain, Taiwan, Ukraine, U.S.A	At screening, 40% had an acute episode 24% were stable on risperidone 35% were stable on another antipsychotic. Median number of manic episodes: 3 Median number of depressive episodes: 2	NR/NR/303 enrolled in DB phase	NR/NR/275 analyzed for efficacy; 303 analyzed for safety

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Morozova; Ortho NCT00132678-2007 Austria, India, Malaysia, Poland, Russia, Slovakia, Spain, Taiwan, Ukraine, U.S.A	77% of subjects in the risperidone long-acting injectable group received a mode dose of 25 mg during DB phase. Placebo vs Risperidone long-acting injectable: Median time to relapse during DB phase was 219 days in placebo, but could not be defined for risperidone because <50% of subjects had experienced a relapse. 25th percentile of time to relapse (time point at which 25% of subjects experienced relapse): 82 vs 173 days Kaplan-Meier estimates of 9-month relapse rate: 60% vs 30%.	Clinical lab tests, vital signs, weight and BMI, ECGs, physical exams, Extrapyramidal Symptoms Rating Scale

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Morozova; Ortho NCT00132678-2007 Austria, India, Malaysia, Poland, Russia, Slovakia, Spain, Taiwan, Ukraine, U.S.A	3 subjects died during the study: 1 due to duodenal ulcer perforation and peritonitis, during open-label oral risperidone; 2 deaths during open-label risperidone long-acting injectable stabilization (Period III) - 1 suicide and 1 accidental death from a fall. AEs during DB phase, risperidone long-acting injectable vs. placebo: Depression 6% vs 2% Weight increase 5% vs 1% Mania 5% vs 11% Bipolar 1 disorder 2% vs 7% Agitation 1% vs 5% Irritability 1% vs 4%Suicide/self-injury 2% vs 3% Serum prolactin concentration change from baseline, ng/mL Increased 17.1 ng/mL during open-label risperidone long-acting-injectable stabilization period, Decreased by 8.8 ng/mL with risperidone long-acting injectable in DB phase Weight increase (>=7%) from baseline during DB phase: 11.6% risperidone long-acting injectable vs 2.8% placebo	Total withdrawals NR. 2 withdrew due to AEs during DB phase	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Muzina 2008 DB RCT Sub analysis of Keck 2006 28 of 161	RCT Multicenter	Inclusion- DSM IV bipolar I age 18 years or more, could provide written consent, who were rapid cyclers for this analysis Exclusions- Pregnancy or lactation, cognitive disorder, schizophrenia, schizoaffective disorder. Psychotic symptoms explained by other medical condition or substance abuse. Cocaine use Allergy/hypersensitivity to aripiprazole or quinolinone, neuroleptic malignant syndrome, seizure disorder. Clinical trial in past month, electroconvulsive therapy within 2 month	An open-label stabilization phase (aripiprazole monotherapy: 15 or 30 mg/day, 6-18 weeks) then randomized to aripiprazole or placebo for 26 weeks and patients completing 26 weeks treatment without relapse could continue for a further 74 weeks.	Stabilization 6-18 weeks
Namjoshi, 2004 United States	RCT	336 patients with bipolar I disorder, manic or mixed, were enrolled in a double-blind, randomized, controlled trial. The majority of the patients were enrolled were recruited from outpatient settings.	(N= 224) Olanzapine (5-20 mg) or (N= 112) Placebo: both added to Lithium or Valproic Acid	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Muzina 2008 DB RCT Sub analysis of Keck 2006 28 of 161	Lorazepam and anticholinergic agents	The primary endpoint was time to relapse for a manic, mixed, or depressive episode (defined by discontinuation caused by lack of efficacy). During double blind phase assessments occurred at day 1, weekly for 4 weeks then every other week until 100 weeks.	Placebo vs. aripiprazole Mean ± SD age (years) 38.8 ± 11.8 vs. 37.6 ± 12.5 Gender, n (%) Male 4 (28.6) vs. 5 (35.7) Female 10 (71.4) vs. 9 (64.3) Race, n (%) White 12 (85.7) vs. 9 (64.3) Hispanic 2 (14.3) vs. 3 (21.4) Other 0 vs 2 (14.3)
Namjoshi, 2004 United States	NR	Young Mania Rating Scale (Y-MRS), Hamilton Rating Scale for Depression (HAM-D) Lehman Brief Quality of Life Interview (QLI)	Mean age: 40.7 years, 52% Male, 86% Caucasian

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Muzina 2008 DB RCT Sub analysis of Keck 2006 28 of 161	Placebo vs. aripiprazole Mean ± SD body weight 88.7 ± 14.9 vs.. 95.5 ± 18.5 Mean ± SD YMRS total score 2.0 ± 2.1 vs..3.6 ± 3.1 Mean ± SD MADRS total score 3.5 ± 3.1 vs. 4.7 ± 4.0	633 recruited 567 stabilization phase 161 entered RCT and 28 included in this analysis	94/ NR/28
Namjoshi, 2004 United States	NR	NR/NR/336	NR/NR/273

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Muzina 2008 DB RCT Sub analysis of Keck 2006 28 of 161	Time to relapse was significantly longer with aripiprazole vs. placebo at week 26 [log-rank p = 0.033; 26-week hazard ratio = 0.21 (95% CI: 0.04, 1.03)] and week 100 [log-rank p = 0.017; 100-week hazard ratio = 0.18 (95% CI: 0.04, 0.88)]. YMRS total score (LOCF) aripiprazole vs. placebo week 26 (+3.0 ± 2.0 vs. +6.6 ± 2.0; p = 0.213; effect size 0.506) week 100 (+2.6 ± 2.6 vs. +9.5 ± 2.6; p = 0.077; effect size 0.730).	Patient reported AEs and adverse events were coded using the Coding Symbol for Thesaurus of Adverse Reaction Terms Extrapyramidal symptoms were assessed using the Simpson-Angus Rating Scale and the Abnormal Involuntary Movement Scale and BARS
Namjoshi, 2004 United States	Lehman Quality of Life scores over 6 weeks: Mean change OLZ vs mean change PBO general life satisfaction: 0.35 vs 0.00; P=0.04 satisfaction with daily activities: 0.34 vs -0.29; P<0.01 satisfaction with living situation: 0.31 vs -0.17; P<0.01 satisfaction with family contact: 0.51 vs 0.07; P=0.01 satisfaction with finances: 0.17 vs -0.07; P=0.10 satisfaction with health: 0.28 vs -0.03; P=0.07 satisfaction with job: -0.05 vs -0.23; P=0.30 satisfaction with social relations: 0.28 vs -0.14; P=0.01 satisfaction with safety: 0.12 vs 0.04; P=0.78 Y-MRS totals: -14.84 vs -11.22; P<0.01 HAM-D totals: -5.52 vs -1.90; P<0.01	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Muzina 2008 DB RCT Sub analysis of Keck 2006 28 of 161	Placebo (14) vs. aripiprazole (14) During 26-week, double-blind phase Anxiety 1 (7.1) vs 4 (28.6) Depression 1 (7.1) vs 3 (21.4) Headache 1 (7.1) vs 2 (14.3) Asthenia 0 vs 2 (14.3) Extremity pain 0 vs. 2 (14.3) Neck rigidity 0 vs. 2 (14.3) Insomnia 0 vs. 2 (14.3) Tremor 0 vs. 2 (14.3) Emotional lability 0 vs. 2 (14.3) Nervousness 0 vs. 2 (14.3) Dental disorder 0 vs. 2 (14.3) During 74-week, double-blind extension phase Upper respiratory infection 1 (7.1) vs. 3 (21.4) Sinusitis 0 vs. 4 (28.6) Infection 1 (7.1) vs. 2 (14.3) Akathisia 1 (7.1) vs. 2 (14.3) Insomnia 2 (14.3) vs. 0 Urinary tract infection 0 vs. 2 (14.3) Pharyngitis 0 vs. 2 (14.3) Flu syndrome 0 vs. 2 (14.3) Diarrhea 0 vs. 2 (14.3) Dry mouth 0 vs. 2 (14.3) Acne 0 vs. 2 (14.3) Mean ± SE weight change week 26 was -3.8 ± 3.4 kg with aripiprazole (n = 11) and +0.3 ± 4.1 kg with placebo (n = 9) (p = 0.444; LOCF). At week 100, mean ± SE weight change -4.6 ± 2.7 kg with aripiprazole (n = 11) and +0.8 ± 3.4 kg with placebo (n = 7) (p = 0.230; LOCF).	At 26 weeks 16 withdrawals 1 due to AEs At 100 weeks 25 withdrawals 1 due to AEs	post hoc analysis
Namjoshi, 2004 United States	NR	71% completed study: withdrawals, lost-to-follow-ups NR	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Nejtek 2008 Texas, USA	DB RCT 2 psychiatric centers	Men and women, 20-50 years, concurrent DSM-IV-defined bipolar I or II disorder and cocaine or methamphetamine dependence.	Monotherapy quetiapine 303.6 +/- 151.9 mg/day risperidone 3.1 +/- 1.2 mg/day . 20 weeks	None
Nierenberg 2006 UK - The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)	Open label RCT Multicenter	18 years or older, met criteria for bipolar disorder type I or II with a current DSM-IV major depressive episode of at least 8 weeks before pathway entry, and had not responded to treatment in first 12 weeks of standard or randomized care pathways for bipolar depression, or had a well-documented failure (e.g., a medical chart was available) to respond to at least two trials of antidepressants or an antidepressant and mood stabilizer regimen	Lamotrigine, inositol, or risperidone for up to 16 weeks in addition to their current open-label mood stabilizer treatment with active antidepressant(s). Lamotrigine versus risperidone (N=17), lamotrigine versus inositol (N=31), or risperidone versus inositol (N=21)	No/No

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Nejtek 2008 Texas, USA	Allowed to enter study with up to 2 psychotropics and treatments for general medical condition i.e. hypertension treatments, acute antibiotics and OTC cold and allergy medications	YMRS, IDS-C-30, SCQ-10 at baseline and then weekly	Quetiapine vs. Risperidone Age 52 (25) vs.. 54 (25) White (%) 71 vs.. 70 Black (%) 29 vs. 24 Hispanic (%) 0 vs. 6
Nierenberg 2006 UK - The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)	Any adjunctive medication deemed necessary for appropriate clinical management, except additional antidepressant medication	The primary outcome measure was the rate of recovery, defined as no more than two symptoms meeting DSMIV threshold criteria for a mood episode and no significant symptoms present for 8 weeks.	39% female 62 % white

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Nejtek 2008 Texas, USA	Quetiapine vs. Risperidone Bipolar 1 79% vs. 89% Bipolar 2 21% vs. 11% Duration of illness yrs 24.7 vs.. 23.3	651/NR/124	80 (32 quetiapine and 34 risperidone)/25/80
Nierenberg 2006 UK - The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)	Lamotrigine vs risperidone Bipolar subtype Bipolar I: 29% Bipolar II: 58.8% Other: 5.9% SUM-D score: 7.6 SUM-M score: 1.3 Global Assessment of Functioning score: 51.7 Clinical Global Impression rating: 4.3 Age: 33.5 years	NR/NR/66	NR/NR/66

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Nejtek 2008 Texas, USA	Most results in graphs Kaplan -Meier survival analyses Quetiapine vs. Risperidone YMRS <9 at 3 weeks 40% vs. 24% IDS-C-30 remission by 6 weeks 40% vs. 50% 51% abstained from drug use during the intervention	PRD-III, weight and BP weekly, cataract opacity every 2 to 4 weeks and ECGs at baseline, every 8 to 11 weeks and at exit
Nierenberg 2006 UK - The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)	At 8 weeks overall recovery rate with lamotrigine was 23.8%, whereas the recovery rates with inositol and risperidone were 17.4% and 4.6%, respectively Duration in study weeks lamotrigine 12.2 risperidone 5.8 and inositol 8.6	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Nejtek 2008 Texas, USA	Quetiapine vs. Risperidone Dizziness 2 vs. 1 Clumsiness 2 vs. 2 Blurred vision 1 vs. 3 Headache 3 vs. 3 Nervousness 7 vs. 3 Nausea or vomiting 2 vs. 1 Sexual difficulties 3 vs. 3 Diarrhea 1 vs. 1 Constipation 1 vs. 0 Dry mouth 3 vs. 1 Decreased appetite 3 vs 3 Increased appetite 6 vs 2 Tiredness 9 vs 6 Increased perspiration 1 vs 1 Daytime sleepiness 6 vs 5	80 withdrawals, none due to AEs	
Nierenberg 2006 UK - The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)	Total AEs lamotrigine 14.3% risperidone 12.5% and inositol 12.5% Serious AEs lamotrigine 5% risperidone 8.3% and inositol 8.3%	NR	See Sachs GS, Thase ME, Otto MW, Bauer M, Miklowitz D, Wisniewski SR, Lavori P, Lebowitz B, Rudorfer M, Frank E, Nierenberg AA, Fava M, Bowden C, Ketter T, Marangell L, Calabrese J, Kupfer D, Rosenbaum JF: Rationale, design, and methods of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2003; 53:1028–1042

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Perlis, 2007 USA	RCT, DB. Multicenter	18-70 years old; YMRS => 20; DSM-IV criteria for bipolar I disorder, manic or mixed episode, without psychotic features. Exclusion- serious suicide risk; DSM-IV substance abuse w/in 2 months (except caffeine and nicotine); current hospitalization > 3 weeks; >= 90 days current manic or mixed episode: previous failure to study drugs in past.	Olanzapine (5-20 mg/day; N = 165) and risperidone (1-6 mg/day; N = 164) 3 weeks	2-5 wash out
Potkin, 2005 United States, Brazil, and Mexico.	RCT, DB inpatient multicenter	Inclusion- Inpatients 18 years or older who had a primary diagnosis of bipolar I disorder. Exclusion- primary DSM-IV Axis I psychiatric disorder diagnosed as schizophrenia or schizoaffective disorder, bipolar I disorder with current episode depressed, or with DSM-IV-defined psychoactive substance abuse/dependence (including alcohol) in the preceding 2 months, substance-induced psychotic disorder or behavioral disturbance, clozapine within 12 weeks, a depot antipsychotic within 4 weeks, or a monoamine oxidase inhibitor within 2 weeks, baseline levels of lithium >0.2 mEq/L, valproate >50 µg/mL, or carbamazepine >4 µg/mL, mental retardation or who were judged by the investigator as being at imminent risk for suicide or homicide.	Oral ziprasidone 80 to 160 mg/d or placebo fo	Run-in 3-10 days

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Perlis, 2007 USA	Benztropine mesylate and lorazepam	Mean change in the Young Mania Rating Scale (YMRS) total score; also HAM-D-21, MADRS, the Clinical Global Impressions-Bipolar Version (CGI-BP) severity of illness scale, and the Cognitive Test for Delirium (CTD). Quality of life (Short Form Health Survey [SF-12]), psychological well-being (Psychological General Well-Being [PGWB] inventory), and sexual functioning were also compared.	Mean age 38 years 45.3% male 73.6 white
Potkin, 2005 United States, Brazil, and Mexico.	Lorazepam and temazepam	Schedule for Affective Disorders and Schizophrenia-Change Bipolar Scale (SADS-CB). SADS-CB-derived Mania Rating Scale (MRS) total score was the primary efficacy parameter. Secondary SADS-CB-derived efficacy parameters included Manic Syndrome and Behavior and Ideation Subscales, Hamilton Depression Rating Scale (HAM-D), and the Montgomery Asberg Depression Rating Scale (MADRS). The Clinical Global Impression-Severity Scale (CGI-S), the Global Assessment of Functioning (GAF), and the Positive and Negative Syndrome Scale (PANSS)	Mean age: ziprasidone 38.9 yrs placebo 39.0 yrs ziprasidone 48.9% male placebo 54.5% male Ethnicity ziprasidone 64% white 19.4% black 16.5% other placebo 58% white 34% black 18% other

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Perlis, 2007 USA	Bipolar subtypes (% patients) Mixed: 58.7 Rapid cycling: 45.3 Mean scale scores CGI-BP=4.4 YMRS=26.6 HAM-D-21: 15.8 MADRS=16.3	NR/329/329	90/16/329
Potkin, 2005 United States, Brazil, and Mexico.	Duration of current episode: 1 month Time since initial onset of symptoms (years): 14.8 Number of prior hospitalizations: 4.7	280/NR/206	85/NR/202

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Perlis, 2007 USA	Between treatments, there was no difference in mean change in the YMRS, MADRS, CTD, PGWB, or SF-12 measures or in remission or response rates Olanzapine vs. risperidone Study completers 78.7% vs. 67.0%; p = .019	Patient interview and modified Simpson-Angus and Barne Akathisia scale.
Potkin, 2005 United States, Brazil, and Mexico.	Ziprasidone vs. placebo Baseline-to-endpoint mean changes MRS scores -11.1 vs. -5.6 P < 0.01 Manic Syndrome Score -5.61 vs. -3.05 P <= 0.01 , CGI-S score -1.09 vs. -0.43 P <= 0.001 PANSS Total -12.01 vs. -3.55 P <= 0.01 and Positive Subscale -5.03 vs. -1,45 P <= 0.001 GAF 15.82 vs. 7.59 P <= 0.001	Observed and reported EPS via Simpson-Angus Rating Scale (SAS), Barnes Akathisia Rating Scale (BAS), and Abnormal Involuntary Movement Scale (AIMS)

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Perlis, 2007 USA	Olanzapine vs. risperidone (%) Sedation 31.5 vs. 27.4 Headache 12.7 vs. 15.2 Dry mouth 28.5 vs. 14.0 Appetite increase 13.9 vs. 11.0 Dizziness 13.9 vs 11.0 Akathisia 7.9 vs. 10.4 Weight increase 16.4 vs. 3.7	Total withdrawals 90 due to AEs 23	
Potkin, 2005 United States, Brazil, and Mexico.	Ziprasidone vs. placebo (%) TRAEs 64.7 vs. 40.9 Somnolence 22.3 vs. 6.1 Headache 12.2 vs. 7.6 EPS 10.8 vs. 1.5 Dizziness 10.1 vs. 1.5 Akathisia 9.4 vs. 4.5 Tremor 7.9 vs. 1.5 Nausea 6.5 vs. 1.5 Asthenia 5.0 vs. 1.5 Abdominal pain 1.4 vs. 7.6	Withdrawals 85 - ziprasidone 55 placebo 30 due to AEs 9 - Ziprasidone 8 placebo 1	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Riesenberg; Ortho NCT00309686-2007 47% of sujbects in USA, 23% in Russia, other countries not specified	DB RCT Multicenter	Males or females aged 18-65 with DSM-IV diagnosed Bipolar I Disorder, most recent episode manic or mixed at screening; with history of at least 1 documented manic or mixed episode requiring medical treatment within 3 years of screening; had a total score of >=20 on YMRS at screening and baseline; and had taken the mood stabilizers lithium or valproate as part of their treatment for Bipolar I Disorder for a minimum of 2 weeks prior to randomization.	6-week DB phase Oral paliperidone ER, flexibly dosed (3 to 12 mg/day) Placebo, flexibly dosed Once daily, added to the mood stabilizers lithium or valproate.	7-day washout of antimanic and mood-stabilizing tx other than lithium or valproate.
Sachs, 2002 USA	RCT, DB, placebo-controlled	Subjects were patients aged 18-65 years with a history of bipolar disorder and at least one prior manic episode who were hospitalized for treatment of manic episode in one of 20 centers. Inclusion criteria included a minimum score of 20 on the Young Mania Rating Scale and a DSM-IV diagnosis of bipolar disorder, with the most recent episode manic or mixed. Patients had to be medically stable according to a pretrial physical examination, medical history, and electrocardiography.	Adjunctive risperidone 2-6 mg/day haloperidol 4-12 mg/day placebo Duration: 3 weeks	NR/ 3 days

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Riesenberg; Ortho NCT00309686-2007 47% of sujbects in USA, 23% in Russia, other countries not specified	For subjects who were not taking valproate or lithium, lithium or valproate was initiated at start of screening and extended up to 2 weeks, including 7 days of washout.	YMRS, GAF, CGI-BP-S, PANSS, SF-36, and Sleep VAS Assessed at Day 42 or at early withdrawal (LOCF); followup visit 1 week after.	NR
Sachs, 2002 USA	Lithium or divalproex allowed	Young Mania Rating Scale (YMRS) CGI severity scale CGI change scale	Mean age: 42.7 years 51.4% male Ethnicity NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Riesenberg; Ortho NCT00309686-2007 47% of sujbects in USA, 23% in Russia, other countries not specified	33% most recent episode mixed 67% most recent episode manic 38% received lithium as the mood stabilizer 62% received valproate	438 screened/ NR eligible/ 300 enrolled	NR/NR/ 299 analyzed
Sachs, 2002 USA	Severity of current manic episode -severe: 54.3% Episode type- manic: 78.6%	180/NR/158	63/8/155

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Riesenberg; Ortho NCT00309686-2007 47% of sujbects in USA, 23% in Russia, other countries not specified	No statistically significant difference between paliperidone ER and placebo in YMRS at 6-week endpoint (p=0.160). Mean (SD) change from baseline to endpoint in YMRS: Paliperidone ER: 014.3 (10.01) Placebo: -13.2 (10.91) No significant difference between groups in % of responders. No significant difference between groups in GAF, CGI-BP-S, PANSS, sleep VAS, and SF-36.	Clinical labs, vital signs, weight, waist circumference, BMI, ECGs, physical exam, rating scales for EPS, MADRS, and Scale for Suicidal Ideation
Sachs, 2002 USA	Risperidone (n=51) vs haloperidol (n=50) vs placebo (n=47) YMRS, change from baseline at endpoint; -8.2(10.4) vs -14.3(9.7) vs -13.4(10.0) risperidone vs placebo, p=0.009 haloperidol vs placebo, p<0.03 risperidone vs haloperidol, p=0.76 CGI severity, ratings of much or very much improved: 27(53%) vs 25(50%) vs 14(30%) risperidone vs placebo, p=0.002 haloperidol vs placebo, p=0.003 risperidone vs haloperidol, NR	Extrapyramidal Symptom Rating Scale

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Riesenberg; Ortho NCT00309686-2007 47% of sujbects in USA, 23% in Russia, other countries not specified	12 (8%) in paliperidone and 2 (1%) in placebo withdrew, mostly due to psychiatric disorders. 1 gastrointestinal hemorrhage occurred, group not specified. Daytime drowsiness (sleep VAS) was increased in paliperidone ER group (p=0.021) AEs more common in paliperidone ER group than placebo were somnolence, akathisia, extrapyramidal disorder, weight increase, and increased appetite. Paliperidone ER vs placebo: Depression: 1.3% vs 1.3% Extrapyramidal disorder: 4% vs 1% Akathisia: 8% vs 1% Received anticholinergics during DB phase: 10% vs 3% Glucose-related AE (NOS): 1.3% vs 0% Potentially prolactin related AE: 0.67% vs 0% Abnormally high heart rates: 12% vs 5% Weight increase >=7%: more common in paliperidone ER than placebo, results NR	Total withdrawals NR 14 (4.7%) withdrew due to AEs	
Sachs, 2002 USA	Risperidone vs haloperidol vs placebo total: 42(81%) vs 49(92%) vs 43(84%) somnolence: 13(25%) vs 16(30%) vs 6(12%) headache: 11(21%) vs 8(15%) vs 12(24%) dyspepsia: 9(17%) vs 9(17%) vs 9(18%) extrapyramidal disorder: 7(13%) vs 15(28%) vs 2(4%) dizziness: 7(13%) vs 4(8%) vs 1(2%) constipation: 3(6%) vs 6(11%) vs 2(4%) tremor: 2(4%) vs 6(11%) vs 2(4%) weight chance (lb): 5.3(7.0) vs 0.3(5.4) vs 1.1(4.8)	Risperidone vs haloperidol vs placebo Total withdrawals: 25 vs 18 vs 28 Withdrawals due to AEs: 2 vs 2 vs 1	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Sachs, 2004 United States *Fair quality*	RCT, DB Multicenter Parallel Setting: patients were required to remain in the hospital for the first 7 days of the randomized period. After this time, they could be treated as either inpatients or outpatients as clinically indicated	Adult patients (≥ 18 years) hospitalized for a DSM-IV diagnosis of bipolar I disorder, most recent episode manic, who had been treated with lithium or divalproex for at least 7 of the 28 days immediately prior to randomization (day 1). A history of at least one documented manic or mixed episode prior to the episode responsible for the current hospitalization was required for selection. At screening and randomization, subjects were selected who had a YMRS score of ≥ 20, with a score of ≥ 4 on 2 of the 4 core YMRS items of irritability, speech, content, and disruptive/aggressive behavior. Patients were also required to have a score of at least 4 for overall bipolar illness on the CGI-BP.	Adjunctive Quetiapine (Q) 100 mg/day at day 1, 200 mg/day at day 2, 300 mg/day at day 3, and 400 mg/day at day 4, dose adjusted to optimize efficacy and tolerability between 200 and 600 mg/day at day 5 and 200 and 800 mg/day at days 6 to 21; mean last week dose was 504 mg/day Placebo (P) All patients began or continued treatment with lithium or divalproex within the established therapeutic range (0.7-1.0 mEq/L for lithium and 500-100 µg/mL for divalproex)	NR/NR
Sachs, 2006 United States	RCT Multicenter	In-patients with DSM-IV diagnosis of Bipolar Disorder, aged 18 and over, with acute manic or mixed episodes, in current acute relapse requiring hospitalization, Young Mania Rating Scale score of >20 . Exclusion: pregnancy, lactation, diagnosed with dementia, delirium, amnestic or other cognitive disorders, schizophrenia/schizoaffective disorder, in first manic episode, under 4 weeks of duration of manic episode, unresponsive to clozapine, possibility of requiring prohibited concomitant therapy, use of psychoactive substances, substance abuse disorder, serum concentrations of lithium >0.6mmol/L or divalproex sodium >50g/mL at screening, risk of suicide/homicide, history of neuroleptic malignant syndrome or seizure disorder, clinically significant abnormal lab tests, vital signs or ECG, previous enrollment in aripiprazole study.	Aripiprazole 30mg daily vs placebo, duration: 3 weeks	NR/NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Sachs, 2004 United States *Fair quality*	Lorazepam: ≤ 6 mg/day from screening to the day prior to randomization, 4 mg/day from days 1 to 4, 2 mg/day from days 5 to 7, and 1 mg/day from days 8 to 10 Zolpidem: max dose 10 mg/day Chloral hydrate: max dose 2 g/day Zaleplon: max dose 20 mg/day IM haloperidol used for severe agitation only during the screening period	Assessments were performed at baseline and days 4, 7, 10, 14 and 21 Primary: Mean change in YMRS total score at the final assessment Secondary: YMRS response rate (% patients with ≥ 50% decrease from baseline in the YMRS score; clinical remission (end-point YMRS score ≤ 12; change from baseline in CGI-BP Severity of Illness score; CGI-BP Global Improvement scale score; MADRS total score; PANSS total score and Activation and Supplemental Aggression Risk subscale scores; GAS score	Mean age=40.5 43.5% female Ethnicity nr
Sachs, 2006 United States	Lorazepam allowed on days 1-4(<6mg/day), 5-7 (<4mg/day) and 8-10 (<2mg/day)	CGI-BP Severity of Illness (mania, depression and overall), PANSS (hostility, positive, negative subscales and total scores)	Mean age: 38.8 years 49% Male White: 72%; Black: 21%, Asian/Pacific Islander: 1% ; Hispanic/Latino: 5%; Other:1%

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Sachs, 2004 United States *Fair quality*	Weight (kg): 87.2 BMI (kg/m2): 29.6 Mean YMRS: 31.3 Episode type (%) Manic moderate: 34.7 Manic severe without psychotic features: 22.9 Manic severe with psychotic features: 42.4 Known duration of illness (mean years): 17.8 Number of manic/mixed episodes during lifetime/past year: 8/1 Number of depressive episodes during lifetime/past year: 5/0	NR/NR/191	85 (44.5%) withdrawn/4 (2.1%) lost to fu/170 analyzed (Q n=81, P n=89)
Sachs, 2006 United States	Mean age current episode began (yrs): A: 37.2 s placebo: 40.3 Rapid cycling: A: 19% vs placebo: 16%	NR/NR/272	3/NR/269

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Sachs, 2004 United States *Fair quality*	Q vs P YMRS Total Score Mean Change: -13.76 vs -9.93, p=0.021 YMRS Response (% patients): 54.3 vs 32.6, p=0.005 YMRS remission (% patients): 45.7 vs 25.8, p=0.007 CGI-BP Severity of Illness score: -1.38 vs -0.78, p=0.001 CGI-BP Global Improvement response (% rated "much improved" or "very much improved"): 50.6 vs 31.5, p=0.012 MADRS mean change: -3.36 vs -2.79, p=NS PANSS Total: -12.47 vs -10.14, p=NS PANSS Activation: -4.08 vs -2.81, p=NS PANSS Supplemental Aggression Risk: -4.64 vs -2.84, p=0.020 Global Assessment Scale: 15.32 vs 11.49, p=0.075	SAS, BARS Rates of treatment-emergent depression (MADRS score ≥ 18, with an increase from baseline of ≥ 4 at any two consecutive assessments or at the last observation) Patients were examined and questioned on all study days regarding any adverse events. Safety evaluations were based on reports of adverse events, cc medication records, change from baseline to day 21 in clinical laboratory assessments (including hematology and chemistry), vital signs, ECG, physical examination, and weight. Adverse events included any treatment-emergent symptoms or worsening of existing symptoms, new illnesses, or clinically significant changes in laboratory tests, vital signs, weight, or ECG.
Sachs, 2006 United States	Completion rates of study: A: 55% vs placebo: 52% Decrease in YMRS total scores at 3 weeks: A: 12.5 vs placebo: 7.2; p<0.001 Mean scores at 3 weeks: CGI-BP Severity of Illness (mania): A: 4.69 vs placebo: 4.71 CGI-BP Severity of Illness (depression): A: 2.66 vs placebo: 2.59 CGI-BP Severity of Illness (overall): A: 4.70 vs placebo: 4.69 CGI-BP Improvement from baseline (mania): A: 2.63 vs placebo: 3.22 CGI-BP Improvement from baseline (overall): A: 2.81 vs placebo: 3.27 PANSS hostility subscale: A: 10.60 vs placebo: 10.74 PANSS positive subscale: A: 17.51 vs placebo: 18.01 PANSS negative subscale: A: 11.22 vs placebo: 11.08 PANSS total: A: 61.77 vs placebo: 62.49	Patient report, physical exam

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Sachs, 2004 United States *Fair quality*	Somnolence: 36 (40%) vs 10 (10%), p>0.001 Headache: 24 (26.7%) vs 21 (21%), p=NS Dry mouth: 17 (18.9%) vs 4 (4%); p=0.005 Asthenia: 10 (11.1%) vs 3 (3%); p=0.052 Postural hypotension: 10 (11.1%) vs 3 (3%), p=0.052 Dizziness: 9 (10%) vs 6 (6%), p=NS SAS mean change: -1.0 vs -0.3, p=NS BARS mean change: -0.4 vs 0, p=NS Increase in weight (kg): 1.60 vs 0.36, p=nr Proportion of patients with ≥ 7% increase in weight: 3.9% vs 1.2%, p=NS Q=P in ECG parameters Rate of emergent depression: 17.3% vs 13.5%, p=NS	Total withdrawals: 35 (38.5%) vs 51 (51.0%); p=NS Withdrawals due to adverse events: 5 (5.5%) vs 6 (6%), p=NS	
Sachs, 2006 United States	Headache: A: 25% vs placebo: 24.8% Nausea: A: 21.3 vs placebo: 15.*% Somnolence: A: 19.9% vs placebo: 10.5% Akathisia: A: 17.6% vs placebo: 4.5% Dyspepsia: A: 15.4% vs placebo: 6.8% Agitation: A: 14.7% vs placebo: 14.3% Constipation: A: 16% vs placebo: 5.3% Vomiting: A: 11% vs placebo: 7.5% Anxiety: A: 10.3% vs placebo: 8.3% Extremity pain: A: 10.3% vs placebo: 5.3% Lightheadedness: A: 8.8% vs placebo: 10.5% Diarrhea: A: 7% vs placebo: 9.8% Number of patients with clinically significant weight gain after 3 weeks (>7%): A: 1 vs placebo: 5	127; 22- A: 12 vs placebo: 10	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Schering Plough 7501008 Schering Plough 7501009	DB RCT Multicenter: Australia, Czech Republic, India, Korea, Russia, Taiwan, Thailand, U.S.	Inclusion: Primary bipolar I disorder with current manic or mixed episode; male or female aged ?18; history of at least one previous moderate to severe mood episode; YMRS >=20 at screening and baseline; and receiving continuous lithium or valproic acid treatment for at least 2 weeks prior to screening. Exclusion: clinical significant medical conditions or abnormal lab, vital sign, physical exam, or ECG finding; seizure disorder; HIV+; primary diagnosis other than bipolar I disorder; diagnosis of schizophrenia, schizoaffective disorder, borderline personality disorder, antisocial personality disorder, or mental retardation; at risk of harming self or others.	Asenapine sublingual, flexible dose (5 or 10 mg BID; mean daily dose 11.8 mg), N=159. Placebo, N167. 12 weeks Mean duration of treatment: Asenapine 47.3 days Placebo 41.9 days	NR
Schering-Plough, Data on File, Study 7501004 United States, Bulgaria, India, Korea, Malaysia, Philippines, Romania, Russia, and Ukraine	DB RCT Multicenter	Inclusion: adult patients (>18 years of age) with a primary diagnosis of bipolar I disorder; a YMRS score >20 at screening and baseline; a manic or mixed episode that began within 3 months of screening; at least one previous moderate to severe mood episode, with or without psychotic features. .	Flexible dose Sublingual asenapine (5-10 mg) BID vs Placebo BID vs Olanzapine (5-20mg) QD 3 weeks	Run-in up to 7 days

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Schering Plough 7501008 Schering Plough 7501009	NR	YMRS total score at baseline and weeks 3, 6, and 12; percentage of YMRS responders (subjects with a 50% decrease from baseline in YMRS total score). percentage of YMRS remitters (subjects with a YMRS total score of 12 or lower) Time to response on YMRS CGI-BP, MADRS, PANSS total score, PANSS Marder factor subscores, HAM-A, CNS vital signs cognition battery, RDQ, and modified ISST	Mean age 39.3 57.4% male 56.4% Caucasian 16.2% Black 21.2% Asian
Schering-Plough, Data on File, Study 7501004 United States, Bulgaria, India, Korea, Malaysia, Philippines, Romania, Russia, and Ukraine	NR	Change from baseline to Day 21 in the YMRS total score (data given in graph for day 2, day 4, day 7, day 14 and day 21); change in CGI-BP mania severity from baseline to Day 21; the percentage of YMRS responders (defined as patients demonstrating a >50% reduction in YMRS total score from baseline to study endpoint); and the percentage of YMRS remitters (defined as patients with YMRS total scores <12 at study endpoint)	asenapine vs placebo vs olanzapine Mean age (SD): 39.1 (12.26) vs 38.1 (12.49) vs 38.4 (10.82) years Female: 50.3% vs 51% vs 42.9% Caucasian: 56.2% vs 56.1% vs 53.7% Black: 20.5% vs 16.3% vs 20% Asian: 21.6% vs 22.4% vs 21.5% Other: 1.6% vs 5.1% vs 4.9%

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Schering Plough 7501008 Schering Plough 7501009	Bipolar I disorder, manic: 60.7% Bipolar I disorder, mixed: 38.7%	Screened NR Eligible NR 326 enrolled	Withdrawn: 210 (64.4%) Lost to f-up: 38 (11.7%) Analyzed: 318 (97.5%)
Schering-Plough, Data on File, Study 7501004 United States, Bulgaria, India, Korea, Malaysia, Philippines, Romania, Russia, and Ukraine	asenapine vs placebo vs olanzapine Diagnosed with Bipolar I disorder, manic: 69.7% vs 67.3% vs 68.8% Diagnosed with Bipolar I disorder, mixed: 30.3% vs 32.7% s 31.2%	NR/NR/488	146/11/480

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Schering Plough 7501008 Schering Plough 7501009	Asenapine vs. placebo: Change in YMRS total score on day 21: -10.3 vs -7.9; p=0.0257 A statistically significant improvement in YMRS total score was maintained at each visit through day 84.(p<0.05 vs. placebo) At day 84, statistically significant differences in favor of asenapine were observed in YMRS responders, YMRS remitters, CGI-BP severity of mania, and CGI-BP severity of overall bipolar illness (p<0.05). No difference between asenapine and placebo at day 84 in MADRS, CGI-BP depression scale, modified ISST, RDQ, PANSS total score, PANSS Marder factor scores, HAM-A, or CNS Vital Signs Cognitive Battery. Change from baseline to week 52 on the YMRS total score and MADRS score (7501009) were not significantly different between asenapine and placebo. Improvement in efficacy observed during 12 week study were maintained through week 52 suggesting long term maintenance of efficacy. Improvements in PANSS totoal score, CGI-BP mania and HAM-A observed during the 7501008 feeder study were maintained through week 52. No significant changes were observed from baseline in the CGI-BP severity of depression CGI-BP severity of overall bipolar illness, ISST modified total score, RDQ, CNS vital signs Cognitive Battery to Wek 52	NR
Schering-Plough, Data on File, Study 7501004 United States, Bulgaria, India, Korea, Malaysia, Philippines, Romania, Russia, and Ukraine	asenapine vs placebo vs olanzapine Mean change in YMRS score (SE): -11.5 (0.8) vs -7.8 (1.11) vs -14.6 (0.76); *P* <0.007 for asenapine vs placebo and *P* <0.0001 for olanzapine vs placebo YMRS response rate: 42.6% vs 34% vs 54.7%; *P* =0.001 for olanzapine vs placebo YMRS remission rate: 35.5% vs 30.9% vs 46.3%; *P* =0.016 for olanzapine vs placebo	AIMS, BARS, SAR-S

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Schering Plough 7501008 Schering Plough 7501009	Asenapine (N=158) vs placebo (N=166) Sedation: 13.3% vs 6% Somnolence: 11.4% vs 4.2% Hypoesthesia oral: 5.7% vs 0.6% Weight increased: 5.1% vs 0.6% Clinically significant weight gain (>=7%): 19.5% vs 5.2%. Mean weight increase: 2.3 kg vs 0.7 kg Incidence of EPS was low and similar between groups; Akathisia: 3.2% vs 5.4% A shift to higher prolactin at endpoint occurred in more asenapine patients than placebo: 34% vs 20.8%.	Asenapine (N=159) vs. placebo (N=167): Total withdrawals: 61.6% vs 67.1% Withdrawals due to AEs: 15.7% vs 11.4%	
Schering-Plough, Data on File, Study 7501004 United States, Bulgaria, India, Korea, Malaysia, Philippines, Romania, Russia, and Ukraine	asenapine vs placebo vs olanzapine n (%) ≥1 treatment-emergent AE: 140 (75.7) vs 55 (56.1) vs 136 (66.3) Somnolence: 22 (11.9) vs 3 (3.1) 23 vs (11.2) Dizziness: 19 (10.3) vs 2 (2.0) vs 13 (6.3) Sedation: 16 (8.6) vs 3 (3.1) vs 29 (14.1) Weight Increase: 12 (6.5) vs 0 (0.0) vs 19 (9.3) Vomiting: 10 (5.4) vs 2 (2.0) vs 4 (2.0) Increased appetite: 7 (3.8) vs 1 (1.0) vs 13 (6.3) Extrapyramidal symptoms: 19 (10.3) vs 3 (3.1) vs 14 (6.8) --Akathisia: 10 (5.4) vs 3 (3.1) vs 10 (4.9) Mean changes from baseline in laboratory values, metabolic parameters, and vital signs were not of clinical significance.	Total Withdrawals: 146 Withdrawals due to AEs: 34	Inconsistency in reporting of discontinuation due to AEs: reported 28 cases (page 51) and reported 34 cases (Table 1; page 53). The higher number was extracted.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Sheehan 2009 USA	DB RCT 3 university centers	18–65 years of age; had to meet DSM-IV criteria for a lifetime bipolar I, II, or NOS disorder and a lifetime panic disorder or GAD. bipolar symptoms had to be no more than moderately severe (defined as a score of ≤4 on the Clinical Global Impressions Scale for use in Bipolar Illness and his or her anxiety symptoms had to be at least moderately severe (defined as a score of ≥4 on the Clinician Global Impression Severity Scale Exclusion - acute, serious, or unstable medical illness or clinical abnormality, were currently receiving an antimanic or mood stabilizing medication, met DSM-IV substance dependence criteria within the past 6 months, had psychotic symptoms, or were judged clinically to be at a serious risk for suicide.	Risperidone (mean at week 8 2.5±1.1 mg/day) vs. placebo 8 weeks	Washout - discontinue psychotropic drugs 7 days or 4 weeks in the case of fluoxetine and depot antipsychotics.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Sheehan 2009 USA	Benzodiazepine (lorazepam) was allowed as needed in the first 2 weeks of the study up to 2 mg day in the first week and up to 1 mg/day in the second week. During the final 6 weeks, zolpidem (10–20 mg/day) or zaleplon (10–20 mg/day) for insomnia	Outcomes measured at baseline and at weekly visits with the Clinician Global Improvement Scale for Anxiety (CGI-21 Anxiety) (primary efficacy measure), the Sheehan Panic Disorder Scale HAM-A; , the Patient Global Improvement for Anxiety (PGI-21 Anxiety), the Young Mania Rating Scale (YMRS), the Inventory of Depressive Symptoms (IDS), the Clinical Global Impression Scale for Bipolar Disorder (CGI BP), and the Sheehan Disability Scale (SDS)	Mean age 37 yrs 36% male 83% white

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Sheehan 2009 USA	Bipolar I Disorder=97 (87%) Bipolar II Disorder or NOS =14(13%)	NR/NR/111	48/6/102

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Sheehan 2009 USA	Most results in graphs and overall there were no differences Risperidone baseline to endpoint vs. placebo baseline to endpoint IDS 32.1±11.4 to 26.5±15.7 vs. of 31.2±11.8 to 19.5±12.7	Physical, electrocardiogram (EKG), and routine laboratory tests were performed at screen and the EKG and laboratory tests were repeated at study termination. Vital signs, including blood pressure, pulse, height and weight, and adverse events were recorded weekly. Rated weekly for extrapyramidal symptoms (EPS) on the Abnormal Voluntary Movement Scale (AIMS) , the Simpson Angus Scale (SAS), and the Barnes Akathisia Rating Scale (BARS)

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Sheehan 2009 USA	Risperidone vs. placebo % Headache 30 vs. 33 Drowsiness 19 vs. 9 Sedation 6 vs. 5 Fatigue 4 vs. 4 Insomnia 4 vs. 5 Nausea 9 vs. 12 Diarrhea 4 vs. 11 Dry Mouth 9 vs. 11 Muscle stiffness, tension, aches 7 vs. 9 Dizziness 6 vs. 4	48 withdrawals; 3 due to AEs	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Shelton, 2004 United States	RCT, DB	Patients were eligible for participation in the study if they (1) had definite and principal diagnosis of bipolar type I or II disorder, currently in a depressed phase; (2) were free of current psychosis, lifetime history of non-affective psychotic disorder, and history of substance abuse in the past 6 months or substance dependence in the past 12 months; (3) were receiving a clinically acceptable type, dose, and plasma level of a mood-stabilizing agent (i.e.valproate, lithium, or carbamazepine) but were otherwise free of psychotropics or potentially psychoactive herbs; (4) had a score of ≥18 on the 17-item version of the Hamilton Rating Scale for Depression (HAM-D) and 8 or below on the Young Mania Rating Scale (YMRS) at both the screening and baseline visits; and (5) were medically healthy.	Adjunctive and monotherapy Risperidone 1 to 4 mg/d (initiated at 1 mg/d and titrated every week by 1 mg/d up to a max of 4 mg/d) Mean max dose (SD): 2.15 (1.2) mg/d Paroxetine 20-40 mg/d (initiated at 20 mg/d and titrated in 10 mg increments every week up to 40 mg) Mean max dose (SD): 35.0 (21.2) mg/d Risperidone + Paroxetine Mean max dose (SD): risp 1.16 (0.67) mg/d + parox 22.0 (12.3) mg/d 12-week DB	NR / NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Shelton, 2004 United States	All patients continued mood stabilizers; lorazepam 3 mg/d allowed in 1st month of treatment	Primary efficacy outcome: HAM-D (Hamilton Rating Scale for Depression), Secondary measures: YMRS, MADRS, CGI-S, CGI-I, and BDI (Beck Depression Inventory) Assessments made at baseline and then on a weekly or bi-weekly basis	Mean age: 35.6 years 50% male Ethnicity NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Shelton, 2004 United States	Mean baseline scores (SD) HAM-D: 21.5 (3.8) BDI: 27.8 (12.2) MADRS: 17.7 (7.1)	NR/ NR/ 30	11/ 2/ unclear

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Shelton, 2004 United States	Risperidone alone vs Risp+Paroxetine vs Paroxetine alone Mean changes (SD) from baseline to endpoint (LOCF) for these tests: HAM-D: 5.2 (8.7) vs 6.3 (6.5) vs 5.6 (6.5), p=NS MADRS: 4.2 (13.7) vs 5.8 (6.1) vs 7.9 (7.3), p=NS There were no significant difference between groups at any rating point (LOCF) for any assessments (HAM-D, MADRS, BDI< CGI, YMRS, SAS, BAS) except: at 4 weeks, YMRS means scores (SD) showed a small significant difference: Risperidone alone vs Risp+Paroxetine vs Paroxetine alone 1.3 (1.04) vs 2.2 (2.4) vs 0 (risp+parox vs parox, p<0.03) Risperidone alone vs Risp+Paroxetine vs Paroxetine alone Remission (HAMD score ≤7 at endpoint) achieved in 1 patient (10%) vs 3 patients (30%) vs 2 patients (20%), p=NS Response (>=50% improvement in HAMD score at endpoint) occurred in 3 patients (30%) vs 3 patients (30%) vs 2 patients (20%), p=NS	Simpson-Angus Scale (SAS) and Barnes Akathisia Scale (BAS) assessed at baseline and then at weekly or biweekly bases

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Shelton, 2004 United States	Risperidone vs Risp+Paroxetine vs Paroxetine SAS mean scores (SD) : 0.4 (0.5) vs 1.2 (1.3) vs 0, p<0.03 for risp+parox vs paroxetine 1 mild case of hypomania (YMRS score=13) in the paroxetine group AEs reported (# of patients/group): Appetite increase: 2 vs 2 vs 2 Weight gain: 1 vs 4 vs 1 Diarrhea: 2 vs 1 vs 3 GI distress: 2 vs 2 vs 2 Somnolence: 5 vs 2 vs 2 Sexual dysfunction: 0 vs 3 vs 2 Insomnia: 0 vs 1 vs 2 Dry mouth: 1 vs 1 vs 3 Fatigue: 2 vs 1 vs 2 Headache: 1 vs 0 vs 1 Tremor: 1 vs 1 vs 1 Blurred vision: 0 vs 1 vs 0 Dizziness: 0 vs 1 vs 1 Paresthesias: 0 vs 1 vs 0 These AEs were reported by risp=1 vs 0 vs 0 patients: anxiety, constipation, dermatitis, dreaming increased, edema, joint pain, and myoclonus	Total withdrawals: 11/30 patients (36.7%) Total withdrawals by group: Risp-5 patients (50%), Risp+paroxetine - 4 patients (40%), Paroxetine - 2 patients (20%) Withdrawals due to AEs: 5 patients total (50%). (Risp - 1 patient (10%); Risp+paroxetine - 3 patients (30%); Paroxetine - 1 patient (10%)) :	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Shi, 2002 USA, UK, and Spain	RCT, DB	Patients had a diagnosis of bipolar I disorder and currently displayed an acute manic or mixed episode (with or without psychotic features) according to DSM-IV based on the Structured Clinical Interview for DSM-IV-Patient Version and had a baseline Young-Mania Rating Scale total score of >= 20.	Olanzapine 15 mg/day Haloperidol 10 mg/day Duration: 12 weeks	NR/ 2-7 days

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Shi, 2002 USA, UK, and Spain	Benzodiazepine, anticholinergic, lorazepam, benzatropine mesylate, biperiden as needed	Young Mania Rating Scale (YMRS) Hamilton Rating Scale for Depression (HAM-D) Health-related quality of life (HRQOL)	Mean age: 39.2 years 39.2% male 46.3% Caucasian

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Shi, 2002 USA, UK, and Spain	SF-36 summary scores- physical: 52.76 SF-36 summary scores- mental: 44.45 patients in work: 47.4%	NR/NR/453	NR/NR/304

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Shi, 2002 USA, UK, and Spain	olanzapine vs haloperidol, p value SF-36 dimension and summary scores, change from baseline at week 6: Dimension scores bodily pain: 3.99(25.46) vs 3.93(23.92), p=0.740 general health: -1.09(20.76) vs -7.36(20.67), p=0.01 mental health: 2.45(21.54) vs -0.96(20.74), p=0.173 physical function: 1.79(24.27) vs -10.96(27.25), p<0.001 role-emotional problem: 6.04(51.51) vs 3.46(58.49), p=0.543 role-physical problem: 3.28(46.93) vs -15.63(46.74), p<0.001 social functioning: 10.95(36.73) vs 2.13(36.48), p=0.036 vitality: -6.66(22.08) vs -14.11(22.85), p=0.002 Summary scores physical: 0.27(9.35) vs -4.27(8.79), p=0.01 mental: 1.5(13.42) vs 0.74(13.35), p=0.58 SF-36 dimension and summary scores, change from baseline at week 12: Dimension scores bodily pain: 5.86(29.12) vs 6.38(23.41), p=0.801 general health: 0.43(23.50) vs -7.69(23.13), p=0.001 mental health: 3.38(24.26) vs -1.17(23.35), p=0.126 physical function: 1.54(26.18) vs -10.46(26.32), p<0.001 role-emotional problem: 18.72(53.19) vs 13.81(58.9), p=0.286 role-physical problem: 6.79(44.76) vs -7.27(46.25), p=0.008 social functioning: 15.82(39.91) vs 10.37(42.41), p=0.171 vitality: -9.5(23.32) vs -17.41(26.66), p=0.004 Summary scores physical: 0.08(9.89) vs -3.66(8.74), p<0.001 mental: 3.5(15.0) vs 2.08(15.71), p=0.327 Work status measurements at week 6: patient in work(%): 31.1 vs 35.8, p=0.403 change in work activities impairment score: -0.16 vs -0.42, p=0.250 change in household activities impairment score: -0.30 vs -0.45, p=0.552 Work status measurements at week 12: change in work activities impairment score: 0.36 vs -0.28, p=0.007 change in household activities impairment score: 0.13 vs -0.28, p=0.023	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Shi, 2002 USA, UK, and Spain	NR	NR	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Smulevich, 2005 International	RCT,DB, Parallel, Multicenter	Eligible pts were physically healthy, aged 18 years or older, and had bipolar I disorder according to DSM-IV criteria and a history of at least one prior documented manic or mixed episode. All pts met DSM-IV criteria for a current manic episode, for which they were voluntarily hospitalized. All pts had a score of >20 on the Young Mania Rating Scale (YMRS) at screening and baseline and a Montgomeray-Asberg Depression Rating Scale (MADRS) of < 20 at baseline.	Risperidone: 1-6 mg/day Haloperidol: 2-12 mg/day or Placebo	3 week run-in/ 3 day washout of any prior psychotropic drug medication
Suppes 2009 North America Trial 127	DB RCT Multicenter	≥18 years of age; DSM-IV diagnosis of bipolar I disorder; ≥1 manic, depressed, or mixed episode in past 2 years; At enrollment, experiencing (or experienced in past 26 weeks) acute; mood episode (DSM-IV) treated with quetiapine with lithium or divalproex (documented by medical records) Achieved ≥12 weeks clinical stability during prerandomization phase following treatment with quetiapine (400–800 mg/day) with lithium or divalproex (Young Mania Rating Scale and MontgomeryÅsberg Depression Rating Scale total scores ≤12)a	Adjunctive quetiapine or placebo, in combination with lithium or divalproex 104 weeks	Run in of 12 stable weeks

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Smulevich, 2005 International	Lorazepam (up to 4 mg/day).	Young Mania Rating Scale (YMRS) Clinical Global Impression (CGI) Global Assessment Scale (GAS) Montgomery-Asberg Depression Rating Scale (MADRS) Brief Psychiatric Rating Scale (BPRS)	Mean age= 39.7 years 53% male 65% Caucasian
Suppes 2009 North America Trial 127	Previous medications for nonpsychiatric medical illnesses, as well as oral contraceptives.	Time to recurrence, YMRS, MADRS Assessed at weekly intervals for weeks 0–2, every 2 weeks for weeks 2–8, at monthly intervals for weeks 8–52, and every 2 months thereafter.	Mean age 40.1 (11.7) % male 47.5 % white 81.7 % black 12.8 % Asian 1.1 % none listed 4.3

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Smulevich, 2005 International	Risperidone vs Haloperidol vs Placebo Psychotic features present: 35.1%vs 34% vs 20% Number of previous manic episodes (mean): 4.6 vs 4.1 vs 4.4 Age at onset of bipolar disorder (mean): 28.9 vs 26.7 vs 27.8	NR/NR/438	NR/NR/386
Suppes 2009 North America Trial 127	Co-treatments % lithium 42.5 % divalproex 57.5 % rapid cyclers 51 YMRS 3.6 (3.1) MADRS 4.8 (3.6)	NR/NR/1953	447/55/623

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Smulevich, 2005 International	Risperidone vs Haloperidol vs Placebo Young Mania Rating Scale mean scores: (YMRS) Week 3: 17 vs 17.4 vs 22.1 Week 12: 11.4 vs 12.9 vs NR Clinical Global Impression mean scores: (CGI) Week 3: 2.3 vs 2.4 vs 2.8 Week 12: 1.6 vs 1.8 vs NR Global Assessment Scale mean scores: (GAS) Week 3: 58.2 vs 57.3 vs 50.9 Week 12: 66.6 vs 63.7 vs NR Montgomery-Asberg Depression Rating Scale mean scores: (MADRS) Week 3: 3.2 vs 4 vs 4.6 Week 12: 4 vs 4.4 vs NR Brief Psychiatric Rating Scale mean scores: (BPRS) Week 3: 25.4 vs 25.7 vs 27 Week 12: 23.9 vs 24.4 vs NR	Patient report, physical exam
Suppes 2009 North America Trial 127	HR time to recurrence 0.32 (95% CI=0.24–0.42, p<0.0001), a risk reduction of 68%. Mood events quetiapine 20.3% [63/310], vs. Placebo 52.1% [163/313] Estimated difference and P (found in online supplement) YMRS –0.78 P < 0.0001 MADRS –0.86 P = 0.0008 CGI-BP, severity of illness subscale –0.14 P = 0.0003 CGI-BP, global improvement subscale –0.05 P = 0.5650 PANSS, positive subscale –0.18 P = 0.0521 Psychological General Well-Being Scale 1.12 P = 0.2664	AEs recorded at each assessment. Adverse events were classified using the Medical Dictionary for Regulatory Activities nomenclature. Laboratory test results (assessed at enrollment, at randomization, and at regular intervals throughout the study), vital signs, weight, body mass index (BMI), ECG results, and physical examination results.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Smulevich, 2005 International	Risperidone vs Haloperidol vs Placebo: Extrapyramidal disorder: Week 3: 17% vs 40% vs 9% Week 12: 24% vs 43% vs NR Somnolence: Week 3: 5% vs 3% vs 1% Week 12: 10% vs 6% vs NR Hyperkinesia: Week 3: 9% vs 15% vs 3% Week 12: 10% vs 19% vs NR Tremor: Week 3: 6% vs 11% vs 6% Week 12: 8% vs 13% vs NR Hypertonia: Week 3: 4% vs 9% vs 0 Week 12: 5% vs 10% vs NR	Withdrawals due to adverse events: risperidone: 6 (4%) haloperidol: 4 (3%) placebo: 7 (5%)	
Suppes 2009 North America Trial 127	Quetiapine + Lithium or Divalproex vs. Placebo + Lithium or Divalproex % Upper respiratory tract infection 11.6 vs 8.0 P = 0.139 Headache 10.0 vs. 13.4 P = 0.213 Nausea 9.7 vs. 11.5 P = 0.516 Insomnia 9.4 vs. 19.5 P < 0.001 Nasopharyngitis 9.0 9.3 P = 1.000 Tremor 8.7 vs. 8.3 P = 0.887 Sedation 7.1 vs. 1.0 P < 0.001 Weight increase 6.8 vs. 2.6 P = 0.013 Hypothyroidism 6.5 vs. 4 1.3 P < 0.001 Vomiting 6.1 vs. 6.1 P = 1.000 Back pain 5.8 vs. 6.7 P = 0.741 Influenza 5.8 vs. 6.1 P = 1.000 Cough 5.8 vs. 3.8 P = 0.267 Diarrhea 5.2 2vs. 8.3 P = 0.150 Arthralgia 5.2 vs. 4.2 P = 0.574	447 withdrawals 43 due to AEs	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Suppes, 2010 United States	DB RCT Multicenter (61 center)	Inclusion: Male and female outpatients, between the ages of 18 and 65 years, with a documented clinical diagnosis of bipolar I or II disorder, most recent episode depressed, as defined by DSM-IV criteria; Patients with or without a rapid-cycling disease course (rapid cycling defined as ≥4 but ≤8 episodes of mood disturbance in the previous 12 months) were eligible for participation. To qualify for enrollment, patients were required to have a total score on HAM-D ≥20, a HAM-D Item 1 (depressed mood) score of ≥2, and a YMRS total score of ≤12 Exclusion: DSM-IV diagnosis of another Axis I disorder that was symptomatic or had required treatment 6 months prior to enrollment; a history of current substance abuse, a history of nonresponse to an adequate trial (6 weeks) of more than two classes of antidepressants during the current episode of depression, a current episode of depression lasting for more than 12 months or commencing less than 4 weeks prior to enrollment, and clinically significant comorbid disease such as uncontrolled diabetes mellitus, renal or hepatic impairment, or coronary artery disease. Patients were excluded from the study if in the investigator's judgment they posed a current serious suicidal or homicidal risk, had a HAM-D17 item 3 score of ≥3, or had attempted suicide within the past 6 months. Female patients were excluded if they were nursing, pregnant, or were of childbearing potential and not using a reliable method of birth control.	Quetiapine XR 300mg qd or placebo qd 8 weeks	washout period of up to 28 days

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Suppes, 2010 United States	The use of nonpsychoactive medications, including over-the-counter medications for the treatment of nonpsychiatric concurrent conditions or illnesses was permitted. Concomitant use of psychoactive drugs was restricted, with the exception of the following: lorazepam (up to 2 mg/day) as rescue medication for severe anxiety; zolpidem tartrate (up to 10 mg/day), zaleplon (up to 20 mg/day), zopiclone (up to 7.5 mg/day), or chloral hydrate (up to 1 g/day) for the treatment of insomnia in instances where treatment was ongoing 28 days prior to enrollment; and anticholinergics for the treatment (but not the prevention) of extrapyramidal symptoms (EPS).	MADRS; CGI - severity of illness and change; assessments conducted at baseline and weekly intervals thereafter.	Mean age: 39.5 years 35.6% male Ethnicity: NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Suppes, 2010 United States	Quetiapine vs Placebo DSM-IV diagnosis, n (%) ---Bipolar I disorder: 107 (80.5) vs 110 (80.3) ---Bipolar II disorder: 26 (19.5) vs 27 (19.5) Rapid cycling, n (%): 36 (27.1) vs 38 (27.7) MADRS total score, mean (SD): 29.8 (5.2) vs 30.1 (5.5) HAM-D total score, mean (SD): 24.8 (3.5) vs 24.6 (3.3) CGI overall bipolar illness score, mean (SD): 4.5 (0.6) vs 4.4 (0.7)	418/NR/280	94/20/270

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Suppes, 2010 United States	Quetiapine vs Placebo Mean changes in MADRS total score: -17.4 vs -11.9; *P* <0.001 Responders (≥50% reduction in MADRS total score): 65.4% vs 43.1%; *P* <0.001 Remitters (MADRS total score ≤12): 54.1% vs 39.4%; *P* =0.018 Improvement in CGI-S score: -1.8 vs -1.2; *P* <0.001	AEs were classified using the Medical Dictionary for Regulatory Activities system of nomenclature. Incidences and withdrawals due to AEs and serious AEs were recorded at each assessment; SAR-S; YMRS; BARS; Columbia Classification codes 1 to 4 (suicide or potential suicide events with suicidal intent determined) were used to indicate suicidal behavior or ideation; Changes from baseline were recorded for clinical laboratory parameters, electrocardiograms, vital signs, and weight.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Suppes, 2010 United States	Quetiapine vs Placebo All AEs: 88.3% vs 68.6% SAR-S - no change: 75% vs 78.8% SAR-S - improvement: 181.% vs 16.4% BARS - no change: 79.3% vs 87.1% BARS - improvement: 16.7% vs 11.4% YMRS score ≥16 on two consecutive assessments or at final assessment: 4.4% vs 6.4% n (%) Dry mouth: 51 (37.2) vs 10 (7.1) Somnolence: 40 (29.2) vs 8 (5.7) Sedation: 32 (23.4) vs 10 (7.1) Dizziness: 18 (13.1) vs 15 (10.7) Increased appetite: 17 (12.4) vs 8 (5.7) Headache: 13 (9.5) vs 14 (10.0) Constipation: 11 (8.0) vs 9 (6.4) Nausea: 10 (7.3) vs 10 (7.1) Weight increase: 10 (7.3) vs 2 (1.4) Dyspepsia: 9 (6.6) vs 1 (0.7) Fatigue: 8 (5.8) vs 3 (2.1) Nasopharyngitis: 6 (4.4) vs 8 (5.7) Insomnia: 3 (2.2) vs 7 (5.0)	Quetiapine vs Placebo Total withdrawals: 52 vs 42 Withdrawals due to AEs: 17 vs 2	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Thase, 2006 USA BOLDER 2	Outpatient, RCT, DB, multicenter	18–65 years; DSM-IV criteria for bipolar I or II disorder and were experiencing a major depressive episode; (HAM-D17-item >= 20 , a HAM-D Item 1 score >= 2; Young Mania Rating Scale (YMRS) score of 12 or less. Exclusion- Axis I disorder other than bipolar disorder that was the primary focus of treatment within 6 months ; a current episode of depression > 12 months or < 4 weeks; nonresponse to an adequate (6 weeks) trial of > 2 classes of antidepressants during the current episode; substance dependence (DSM-IV) or substance use (except for nicotine) within 12 months; a clinically significant medical illness; a current serious suicidal or homicidal risk,	Quetiapine (300 mg/d or 600 mg/d) or placebo 8 weeks	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Thase, 2006 USA BOLDER 2	Over-the-counter and other nonpsychotropic medications taken before study entry were allowed during the study and lorazepam (1–3 mg/d for severe anxiety) and zolpidem tartrate (5–10 mg/d at bedtime for insomnia) were permitted during the first 3 weeks	MADRS;HAM-D: CGI-S and I; SDS;Q-LES-Q Assessments made at baseline then weekly 1-8 HAM-A assessed weeks 1, 4 and 8	Mean age 37 years 43% male 77% white 12% black 1% oriental 10% other

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Thase, 2006 USA BOLDER 2	67% Bipolar I 33% Bipolar II	788/NR/509	208/54/467

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Thase, 2006 USA BOLDER 2	Least Squares Mean Change in Score at Last Assessment (SE) MADRS Placebo 11.93 (0.99) 300 mg/d quetiapine 16.94 (0.99) p < 0.001y 600 mg/d quetiapine 16.00 (1.01) p= 0.001y HAM-D Placebo 9.92 (0.69) 300 mg/d quetiapine 13.81 (0.69) p <0.001 600 mg/d quetiapine 12.97 (0.71) p) <0.001 HAM-D Item 1 Placebo 1.29 (0.10) 300 mg/d quetiapine1.76 (0.10) p <0.001 600 mg/d quetiapine 1.57 (0.11) p <0.05 CGI-Severity Placebo 1.12 (0.12) 300 mg/d quetiapine 1.68 (0.12) p <0.001 600 mg/d quetiapine 1.59 (0.12) p <0.001 CGI-Improvement Placebo 2.88 (0.10) 300 mg/d quetiapine 2.28 (0.10) p <0.001 600 mg/d quetiapine 2.29 (0.11) p) <0.001 HAM-A Placebo 18.2 5.7 5.80 (0.65) 300 mg/d quetiapine 8.78 (0.65) p <0.001 600 mg/d quetiapine 8.15 (0.66) p= 0.001	The incidence and severity of adverse events, as well as withdrawals because of adverse events, were evaluated. The Simpson-Angus Rating Scale (SAS)32 and the Barnes Akathisia Rating Scale (BARS) were used to assess extrapyramidal symptoms and akathisia. Clinical chemistry, hematology, and 12-lead electrocardiograms were also assessed.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Thase, 2006 USA BOLDER 2	Placebo vs. Quetiapine 300 vs. Quetiapine 600 Dry mouth 18 vs. 42.7 vs. 47.0 Sedation 10.2 vs. 32.2 vs. 27.4 Somnolence 4.8 vs. 29.8 vs.29.8 Dizziness 5.4 vs. 14.0 vs. 16.1 Fatigue 7.8 vs. 7.8 vs. 9.4 vs. 11.3 Headache 16.8 vs. 8.8 vs. 8.3 Constipation 3.0 vs. 8.2 vs. 10.0 Nausea 13.2 vs. 7.6 vs. 10.7	Total withdrawals 208 due to AEs 25	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Thase, 2008 United States	RCT Multicenter	Inclusion - male and female outpatients, aged 18 to 65 years, with a diagnosis of bipolar I disorder experiencing a major depressive episode (2 weeks to 2 years in duration) without psychotic features. Clinically significant depressive symptoms were defined by a HAMD total score greater than or equal to 18 with a score Q2 on Item 1 (depressed mood) at both the screening and baseline visits, and a 25% increase or decrease in the total score between those visits. Patients had to have a YMRS score ≤ 12 at both the screening and baseline visits, with a < 4-point increase in total score between those visits. At the time of randomization, patients must have been washed out of all psychotropic medications for their bipolar illness for > 3 days, while continuing to meet entry criteria for depressive symptoms. Women of childbearing potential had to be using an adequate method of contraception to avoid pregnancy throughout and for up to 4 weeks after the study. Exclusion criteria included patients: with a primary psychiatric disorder other than bipolar I disorder with a major depressive episode; with late-onset depression (e.g., beyond the age of 55 years); experiencing their first depressive episode; who experienced Q6 manic and/or major depressive episodes within 12 months before randomization; with a cognitive disorder, psychotic disorder, or borderline or antisocial personality disorder.	Placebo or aripiprazole (initiated at 10 mg/d, then flexibly dosed at 5–30 mg/d based on clinical effect and tolerability) for 8 weeks	3- to 28-day screening period
Tohen 2008 Australia, Greece, Hungary and Russia	DB RCT followed by open label psychiatric or mental health clinics, hospital units, or health research institutes	Men or women, aged 18–65 years, with a diagnosis of DSM–IV bipolar manic or mixed episode (with or without psychotic features)	olanzapine (10–30mg/day) plus carbamazepine (400–1200 mg/day; n=58) placebo plus carbamazepine (n=60) followed by open-label, 20-week olanzapine (10–30 mg/day) plus carbamazepine (400–1200 mg/day, n=86), with	1 week screening/washout

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Thase, 2008 United States	stable doses of benzodiazepines for insomnia or anxiety and anticholinergics for treatment of extrapyramidal symptoms	MADRS, CCGI-BP, response and remission	Mean age 40 years 39% male Ethnicity NR
Tohen 2008 Australia, Greece, Hungary and Russia	limited dose of benzodiazepines (lorazepam 42 mg/day or equivalents), anticholinergics (benzatropine mesilate or biperiden 46 mg/day), and chronic thyroid supplement therapy if they were on a stable dose of the medication for at least 60 days	YMRS, MADRS and CGI-BP, at screening, baseline and every week through DB period	mean age 40.7 yrs % male 42.4 99.2% white

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Thase, 2008 United States	Mean # mood episodes within past 12 months=2.3	NR/NR/749	286/80/695
Tohen 2008 Australia, Greece, Hungary and Russia	98.3% had bipolar mania with a moderate to severe episode.	134/121/118	33 (15 olz+carb, 18 placebo +carb) /0/117

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Thase, 2008 United States	Change in MADRS - no statistical difference in either study, results presented graphically Change in CGI-BP Severity Study 1 placebo 1.10 aripiprazole 1.310 Study 2 placebo 1.19 aripiprazole 1.4 Change in YMRS Study 1 placebo 0.610 aripiprazole -1.00 Study 2 placebo -0.38 aripiprazole -0.88 Study concludes. "In conclusion, aripiprazole used as monotherapy with the implemented dosing regimen did not demonstrate superior efficacy to placebo in patients with bipolar I disorder with a major depressive episode without psychotic features."	adverse event (AE) reporting; Simpson–Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes–Akathisia Rating Scale (BAS) scores; vital signs, laboratory tests, and electrocardiograms; serum prolactin levels; mean change in weight from baseline; and percentage of patients with clinically significant weight gain (>7%).
Tohen 2008 Australia, Greece, Hungary and Russia	olanzapine plus carbamazepine vs. carbamazepine monotherapy Change from baseline to endpoint Least squares mean (s.e..) YMRS total -15.49 (1.07) vs. -15.25 (1.09) CGI–BP overall -1.29 (0.16) vs. -1.35 (0.16) CGI–BP mania -2.05 (0.16) vs. -2.07 (0.16) CGI–BP depression 0.05 (0.12) vs. 0.09 (0.12) MADRS total -1.22 (0.96) vs. -1.00 (0.96)	Adverse events, laboratory values, electrocardiograms (ECGs), vital signs and extrapyramidal symptoms.via the Simpson–Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Thase, 2008 United States	Placebo vs. aripiprazole n(%) Study 1 and study 2 Akathisia 9 (4.8) vs. 49 (27.5) 5 (2.8) vs. 39 (21.4) Insomnia 9 (4.8) vs. 29 (16.3) 20 (11.0) vs. 34 (18.7) Nausea 10 (5.4) vs. 27 (15.2) 14 (7.7) vs. 26 (14.3) Fatigue 8 (4.3) vs. 19 (10.7) 14 (7.7) vs. 23 (12.6) Restlessness 10 (5.4) vs. 18 (10.1) 5 (2.8) vs. 22 (12.1) Dry mouth 5 (2.7) vs. 14 (7.9) 16 (8.8) vs. 22 (12.1) Headache 28 (15.1) vs. 25 (14.0) 31 (17.1) vs. 27 (14.8) Anxiety 5 (2.7) vs. 10 (5.6) 5 (2.8) vs. 17 (9.3) URTI 18 (9.7) vs. 11 (6.2) 5 (2.8) vs. 3 (1.6) Nasopharyngitis 11 (5.9) vs. 8 (4.5) 18 (9.9) vs. 7 (3.8) Diarrhea 11 (5.9) vs. 11 (6.2) 11 (6.1) vs. 14 (7.7) Vomiting 4 (2.2) vs. 11 (6.2) 3 (1.7) vs. 9 (4.9) Constipation 10 (5.4) vs. 7 (3.9) 6 (3.3) vs. 9 (4.9) Increased appetite 4 (2.2) vs. 12 (6.7) 3 (1.7) vs. 8 (4.4) Back pain 3 (1.6) vs. 14 (7.9) 5 (2.8) vs. 8 (4.4) Dizziness 12 (6.4) vs. 12 (6.7) 14 (7.7) vs. 15 (8.2) Somnolence 7 (3.8) vs. 12 (6.7) 8 (4.4) vs. 15 (8.2) Sedation 4 (2.2) vs. 9 (5.1) 4 (2.2) vs. 10 (5.5) Disturbance in attention 0 vs. 3 (1.7) 4 (2.2) vs. 10 (5.5) Irritability 6 (3.2) vs. 7 (3.9) 7 (3.9) vs. 12 (6.6)	286 withdrawal 74 due to AEs	
Tohen 2008 Australia, Greece, Hungary and Russia	olanzapine plus carbamazepine vs. carbamazepine monotherapy Somnolence 9 (15.5) vs. 8 (13.3) Dry mouth 5 (8.6) vs. 1 (1.7) Headache 5 (8.6) vs. 5 (8.3) Alanine aminotransferase increased 4 (6.9)* vs. 0 (0.0) Vision blurred 4 (6.9) vs. 1 (1.7) Dizziness 3 (5.2) vs. 2 (3.3) Rash 3 (5.2) vs. 0 (0.0) Sedation 3 (5.2) vs. 1 (1.7) Nausea 1 (1.7) vs. 4 (6.7) Weight increased 1 (1.7) vs. 3 (5.0) Constipation 0 (0.0)** vs. 6 (10.0) *P=0.05; **P=0.005	33 withdrawn due to AEs 10 (5 in each group)	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Tohen 2008 Mutinational (France, Germany, Lithuania, Puerto Rico, Romania, Russia, and the United States)	DB RCT Multicenter	men or women (inpatient or outpatient), 18 to 65 years, with a diagnosis of DSM-IV acute bipolar manic or mixed episode without psychotic features, plus the rapid cycling item from the bipolar specifiers obtained from the SCID-I.	olanzapine (5–20mg/day), divalproex (500–2500 mg/day), o placebo 3 weeks 9-week double-blind extension of active arms.	2-14 screening period

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Tohen 2008 Mutinational (France, Germany, Lithuania, Puerto Rico, Romania, Russia, and the United States)	limited dose of benzodiazepines (lorazepam ≤ 2 mg/day or equivalents, administered > 8 hours before psychiatric evaluation), anticholinergics (benztropine mesylate or biperiden ≤ 6 mg/day), and ongoing thyroid supplement therapy were permitted.	CGI-BP, YMRS and MADRS, screening, baseline, endpoints	Mean age 39.6 yrs 47% male 81.1% white

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Tohen 2008 Mutinational (France, Germany, Lithuania, Puerto Rico, Romania, Russia, and the United States)	mean ± SD baseline YMRS 23.8 ± 2.7, with having mild mania 21.5% (104/484) moderate mania 78.2% (380/486)	782/606/521	Study period 2 134/29/521 Study period 3 122/24/NR or not clear

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Tohen 2008 Mutinational (France, Germany, Lithuania, Puerto Rico, Romania, Russia, and the United States)	Study period II Olanzapine vs. Divalproex vs. Placebo YMRS total score –9.4 (0.60) vs. –8.2 (0.62) vs. –7.4 (0.80) Olanzapine vs Divalproex P = NS CGI-BP overall score –0.8 (0.07) vs. –0.6 (0.08) vs. –0.5 (0.10) Olanzapine vs Divalproex P = 0.014 CGI-BP mania score –1.0 (0.08) vs. –0.8 (0.08) vs. –0.7 (0.11) Olanzapine vs Divalproex P = 0.038 CGI-BP depression score –0.3 (0.07) vs. –0.2 (0.07) vs. –0.1 (0.09) Olanzapine vs Divalproex P = 0.040 MADRS total score –3.3 (0.46) vs. –2.1 (0.47) vs. –2.4 (0.61) Olanzapine vs Divalproex P = 0.045 **Study period II/III Olanzapine vs. Divalproex No placebo** YMRS total score –13.3 (0.69) vs. –10.7 (0.72) P = 0.004 CGI-BP overall score –1.2 (0.09) vs. –0.9 (0.10) P = 0.023 CGI-BP mania score –1.5 (0.10) vs. –1.2 (0.10) P = 0.008 CGI-BP depression score –0.2 (0.07) vs. –0.2 (0.08) P = 0.910 MADRS total score –2.3 (0.57) vs. –2.2 (0.59) P = 0.883	adverse events (AEs), laboratory values, electrocardiograms, vital signs, and extrapyramidal symptoms. Extrapyramidal symptoms were measured with the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Tohen 2008 Mutinational (France, Germany, Lithuania, Puerto Rico, Romania, Russia, and the United States)	Study period 2 Olanzapine vs. Divalproex vs. Placebo Dry mouth 12 (5.6) vs. 5 (2.5) vs. 3 (2.9) Olanzapine vs Divalproex P = NS Nausea 2 (0.9) vs. 17 (8.5) vs. 3 (2.9) Olanzapine vs Divalproex P < .001 Weight increase 19 (8.8) vs. 8 (4.0) vs, 3 (2.9) Olanzapine vs Divalproex P = 0.016 Increased appetite 12 (5.6) vs. 11 (5.5) vs. 2 (1.9) Olanzapine vs Divalproex P = NS Somnolence 19 (8.8) vs. 5 (2.5) vs. 3 (2.9) Olanzapine vs Divalproex P = .004 Sedation 12 (5.6) vs. 7 (3.5) vs. 5 (4.8) Olanzapine vs Divalproex P = NS Headache 9 (4.2) vs. 18 (9.0) vs. 9 (8.6) Olanzapine vs Divalproex P = NS Insomnia 2 (0.9) vs. 11 (5.5) vs. 4 (3.8) Olanzapine vs Divalproex P = 0.008 Study period 2/3 Olanzapine vs. Divalproex (Placebo not included) Dry mouth 14 (6.5) vs. 7 (3.5) P=NS Diarrhea 4 (1.9) vs. 11 (5.5) P = 0.057 Nausea 3 (1.4) vs. 21 (10.4) P < .001 Vomiting 2 (0.9) vs. 10 (5.0) P = 0.022 Fatigue 13 (6.0) vs. 6 (3.0) P = NS Weight increase 28 (13.0) vs. 12 (6.0) P = 0.003 Increased appetite 17 (7.9) vs. 14 (7.0) P = NS Somnolence 24 (11.2) vs. 8 (4.0) P = 0.004 Sedation 14 (6.5) vs. 8 (4.0) P = NS Headache 16 (7.4) vs. 23 (11.4) P = NS Tremor 4 (1.9) vs. 10 (5.0) P = NS Insomnia 5 (2.3) vs. 13 (6.5) P = 0.053	134 withdrawals, 23 due to AES in extension an additional 122 withdrew, 25 due to AEs	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Tohen, 2003 Tohen 2008 International	RCT Multicenter 13.1% Inpatients	Patients, 18 years or older, that met DSM-IV criteria for bipolar I disorder, depressed; score ≥ 20 on the MADRS; history of at least 1 previous manic or mixed episode of sufficient severity to require treatment with a mood stabilizer or an antipsychotic agent.	Monotherapy Olanzapine 5-20 mg Olanzapine-fluoxetine combination, 6 and 25, 6 and 50 or 12 and 50 mg Placebo 8-week DB	2-14 day washout

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Tohen, 2003 Tohen 2008 International	Benzodiazepines (up to 2 mg of lorazepam equivalents per day) Anticholinergic therapy (benztropine mesylate or biperiden ≥ 6 mg daily or trihexyphenidyl ≥ mg daily)	Primary: MADRS change score Secondary: CGI-BP-S, YMRS, HAS Clinical visits conducted at weeks 1, 2, 3, 4, 6, and 8	Mean age=41.8 63% female 82.6% white

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Tohen, 2003 Tohen 2008 International	Inpatient=13.1% Psychotic features=12.5% Melancholic features=66.7% Atypical features=8.3% Rapid cycling course=37% Manic or mixed episode in past 12 months=80.7% Length of current depressive episode (days)=73	NR/1072/833 Placebo n=377 Olanzapine n=370 Olanzapine+fluoxetine n=86	454/833(54.5%) withdrawn 57/833(6.8%) lost to follow-up 788/833 (94.6%) analyzed

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Tohen, 2003 Tohen 2008 International	Placebo vs olanzapine (week 8) MADRS mean change (points): -15.0 vs -11.9; p=0.002 MADRS response (patients): 39.0% vs 30.4%; p=0.02 Median times to response (days): 59 vs 55; p=0.01 MADRS remission (patients): 32.8% vs 24.5%; p=0.02 Median time to remission (days): 59 vs 57; p=0.02 YMRS mean change (points): -1.4 vs -0.1; p=0.002 CGI-BP-S mean change (points): -1.6 vs -1.2; p=0.004 HAM-A mean change (points): -5.5 vs -3.5; p=0.002 Anticholinergic medication use (% patients): 2.8% vs 3.7%; p=NS Subgroup of patients with comorbid anxiety (week 8) Mean change from baseline in MADRS -11.3 vs -15.7, difference from placebo (95% CI) -4.4 (-7.7 to -1.0) Mean change from baseline in HAS -11.0 vs -15.0, difference from placebo(95% CI) -4.0 (-6.5to -1.5) Mean change from baseline in YRMS -0.3 vs -0.6 Mean difference from placebo (95% CI) -0.9 (-2.3 to 0.5)	Adverse events were coded using the Coding Symbol for Thesaurus of Adverse Reaction Terms Extrapyramidal symptoms were assessed using the Simpson-Angus Rating Scale and the Abnormal Involuntary Movement Scale

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Tohen, 2003 Tohen 2008 International	Olanzapine vs placebo Treatment-emergent mania (% patients with YMRS score ≥ 15): 5.7% vs 6.7%; p=NS EPS symptoms: olanzapine=placebo (data nr) Comorbid anxiety subgroup % Withdrawal due to adverse events: 10.7 vs 4.4	Olanzapine vs placebo Total withdrawals: 51.6% vs 61.5%; p<0.01 Overall deaths: 0 vs 3/377(0.8%); p=NS Withdrawals due to adverse events: 9.2% vs 5.0%; p=0.03 Mean change in cholesterol level (mg/dL): +6 vs -6; p<0.001 Mean change in nonfasting glucose levels (mmol/L): 1.4% vs 0.3%; p=NS Somnolence: 28.1 vs 12.5; p<0.001 Weight gain: 17.3 vs 2.7; p<0.001 Increased appetite: 13.5 vs 5.0; p<0.001 Headache: 12.4 vs 18.6; p=0.03 Dry mouth: 11.1 vs 6.1; p=0.02 Nervousness: 10.5 vs 8.0; p=NS Asthenia: 9.7 vs 3.2; p<0.001 Insomnia: 8.4 vs 15.1; p=0.005 Diarrhea: 6.5 vs 6.6; p=NS Nausea: 4.3 vs 8.8; p=0.02	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Tohen, 2004 United States/Canada Follow-up to HGFU (6-week study of acute therapy)	RCT Multicenter	Men and women aged 18-70 years who had achieved syndrome remission from an index manic or mixed episode during a 6-week study of acute therapy; all patients had been diagnosed with bipolar I disorder, manic or mixed episode, with or without psychotic features (DSM-IV); ≥ two previous mood episodes; documented trial at a therapeutic blood level of lithium (0.6-1.2 mmol/l) or valproate (5-0-125 µg/ml) for ≥ 2 weeks with persistent manic symptoms (YMRS ≥ 16)	Random reassignment at visit 8 of acute phase to Adjunctive Therapy Olanzapine 8.6 mg (mean) or placebo added to lithium (1064.6 mg/1023.8 mg for olanzapine/placebo groups) or valproate (1264.6 mg/1286.5 mg for olanzapine/placebo groups) (patients remained on same mood stabilizer that they had received during the acute phase) 18 months	No/No
Tohen, 2006 Tohen 2009 Unied States and Romania	Open RCT, parallel Multicenter	Inpatients and outpatients aged 18 yeas and older, meeting DSM-IV criteria for Bipolar Disorder, with Young Mania Rating Scale score >20, in current symptomatic remission after open-label treatment with olanzapine, at least 2 prior manic/mixed episodes within the last 6 years of study,	(N= 225) olanzapine, 5-20mg daily vs (N=136) placebo, duration: 48 weeks	3 weeks/NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Tohen, 2004 United States/Canada Follow-up to HGFU (6-week study of acute therapy)	Benzodiazepines (≤ 2 mg lorazepam equivalent per day) for no more than 5 consecutive days or 60 days cumulatively Anticholinergic therapy (benzatropine mesylate ≤ 2 mg per day)	Symptomatic relapse (YMRS ≥ 15 and HAMD-21 ≥ 15) Syndrome relapse (DSM-IV criteria)	Mean age=41.3 48.5% male 84.8% white
Tohen, 2006 Tohen 2009 Unied States and Romania	NR	Young Mania Rating Scale, Hamilton Depression Rating Scale	Mean age: 40.4 years 39% Male Ethnicity NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Tohen, 2004 United States/Canada Follow-up to HGFU (6-week study of acute therapy)	Characteristics of index episode at acute study entry: Mixed episode=49% Without psychotic features=73.7% Rapid-cycling course=41.4%	NR/160/99	78 (78.8%) withdrawn Lost to fu nr 99 analyzed (olanzapine=48; placebo=51)
Tohen, 2006 Tohen 2009 Unied States and Romania	Median Length of current episode: O: 29 days vs L: 27.5 days	931/731/361	90/24/361

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Tohen, 2004 United States/Canada Follow-up to HGFU (6-week study of acute therapy)	Olanzapine vs placebo Time to symptomatic relapse (days): 42 vs 163 (HR 2.29, 95% CI 1.10-4.78) Symptomatic relapse rate (% patients): 37% vs 55%; p=NS Time to syndrome relapse (days): 40.5 vs 94; p=NS Syndrome relapse rate (% patients): 29% vs 31%; p=NS Time to symptomatic relapse into mania alone (days): 171.5 vs 59; p=NS Mania symptom relapse rate (% patients): 20% vs 29%; p=NS Time to symptomatic relapse into depression alone (days): 163 vs 55; p=NS Depression symptom relapse rate (% patients); 23% vs 40%; p=NS	SAS, BARS, AIMS Clinically relevant weight gain (≥ 7% increase)
Tohen, 2006 Tohen 2009 Unied States and Romania	Relapse rate: O: 46.7% vs placebo: 80.1% Rates of relapse requiring hospitalization: O: 2 vs placebo: 7 Study completion rates: O: 21.3% vs placebo: 6.6% Median time to discontinuation of treatment (days): O: 83 vs placebo: 26; p<0.001 Incidence of relapse by type of relapse in patients with mixed index episode Olanzapine vs placebo 59.2% vs 91.1% p<0.001 Depressive: 36.8% vs 44.4% p=0.456 Manic: 11.8% vs 37.8% , p=0.001 Hypomanic: 30.3% vs 31.1% p>0.999 Mixed: 10.5% vs 8.9%, p>0.999 Median time to relapse of any kind : 46 days versus 15 days , p<0.001 Median time to depressive relapse: 85 days vs 22 days (p=0.001) Median time to hypomanic relapse: 224 days vs 57 days (p<0.001) Median time to mixed relapse: too few in olanzapine group to calculate median vs 42 days, p<0.001	Laboratory tests, patient report

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Tohen, 2004 United States/Canada Follow-up to HGFU (6-week study of acute therapy)	Olanzapine vs placebo Depression: 37.3% vs 29.2%; p=NS Somnolence: 19.6% vs 8.3%; p=NS Weight gain: 19.6% vs 6.3% (RR 13.4; 95% CI 0.5 to 26.2) Anxiety: 13.7% vs 14.6%; p=NS Tremor: 13.7% vs 8.3%; p=NS Apathy: 9.8% vs 16.7%; p=NS Asthenia: 9.8% vs 12.5%; p=NS Diarrhea: 9.8% vs 16.7%; p=NS Insomnia: 3.9% vs 27.1%; (RR -23.2; 95% CI -36.8 to -9.5) Abnormal thinking: 2% vs 10.4%; p=NS Changes in EPS scales (mean) SAS: 0.22 vs -0.13 (WMD 0.35; 95% CI 0.01 to 0.68) AIMS: -0.02 vs 0.13; NS BARS: 0.14 vs -0.06; NS Laboratory analyses Weight change (mean kg): 2.0 vs -1.8; (WMD 3.8; 95% CI 1.8 to 5.9) Cholesterol change (mean mmol/L): -0.04 vs -0.06; NS	Olanzapine vs placebo Total withdrawals: 35 (68.6%) vs 43 (89.6%); p=0.014 Withdrawals due to adverse events: 5 (9.8%) vs 8 (16.6%)	
Tohen, 2006 Tohen 2009 Unied States and Romania	Changes in weight: olanzapine: mean gain of 1.0 kg vs placebo: mean loss of 1.0kg Increase in weight of <7%: O: 17.7% vs placebo: 2.2% Dry Mouth: O: 1.85 vs placebo: 0.7% Appetite increased: O: 1.8% vs placebo: 0% Somnolence: O: 2.7% vs placebo: 1.5% Sedation: O: 0.9% vs placebo: 0% Fatigue: O: 6.2% vs placebo: 1.5% Insomnia: O: 2.2% vs placebo: 14% Treatment emergent AE in patients with mixed index episode (phase 2) Weight gain: olanzapine 5.3% vs placebo 2.2% , absolute risk reduction 3.0%, relative risk 2.37, 95% CI (0.27 to 20.54)	90;17	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Tohen, 2008 Multi-center: France, Germany, Lithuania, Puerto Rico, Romania, Russia, and U.S.	DB RCT	Men or women, inpatient or outpatient, aged 18-65 with DSM-IV-TR diagnosed acute bipolar manic or mixed episode without psychotic features; YMRS total score >=20 and <=30 (mild to moderate) and a CGI-BP-S mania subscore of 3 (mild) or 4 (moderate) at screening and randomization; negative test for pregnancy if female; using medically accepted contraception. Exclusions: a rapid-cycling course or presence of pyschotic features.	3 groups: olanzapine (N-215) v. divalproex (N=201) v. placebo (N=105); 3 week acute therapy period. Olanzapine (5-20 mg; mean 11.4 mg/day) was administered orally once daily in the evening. Divalproex (500-2500 mg, mean 848.4 mg/day) was administered orally 2x daily. Placebo was administered orally 3x daily. Placebo capsules were used to balance the treatment regimen into 3 divided doses.	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Tohen, 2008 Multi-center: France, Germany, Lithuania, Puerto Rico, Romania, Russia, and U.S.	A limited dose of benzodiazepines administered >8 hours before psychiatric evaluation; anticholinergics; and ongoing thyroid supplement therapy were permitted.	Baseline to endpoint (week 3) mean change in YMRS total score. MADRS CGI-BP Rates of response and time to response (defined as >=50% reduction in total YMRS score at 3 weeks) Rates of remission, defined as score <=12 on YMRS at week 3.	Mean age 40 44.5% male Ethnicity NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Tohen, 2008 Multi-center: France, Germany, Lithuania, Puerto Rico, Romania, Russia, and U.S.	Current episode mixed: 27% Current episode manic: 62% Episode severity mild: 19% Episode severity moderate: 70% Mean YMRS total score: 23.8 Mean MADRS total score: 10.7 Mean CGI-BP overall score: 3.6 Mean CGI-BP mania score: 3.7 Mean CGI-BP depression score: 2.0	782 screened 606 eligible (i.e. Entry criteria not met" for 176) 521 randomized	134 withdrawn 29 lost to followup 486 analyzed

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Tohen, 2008 Multi-center: France, Germany, Lithuania, Puerto Rico, Romania, Russia, and U.S.	Change from baseline to week 3, LS mean change (SE); p-value for olanzapine vs placebo: Olanzapine (N=201) vs divalproex (N=186) vs placebo (N=99): YMRS total score: -9.4 (0.60) vs -8.2 (0.62) vs -7.4 (0.80); p=0.034 CGI-BP overall score: -0.8 (0.07) vs -0.6 (0.08) vs -0.5 (0.10); p=0.005 CGI-BP mania score: -1.0 (0.08) vs -0.8 (0.08) vs -0.7 (0.11); p=0.031 CGI-BP depression score: -0.3 (0.07) vs -0.2 (0.07) vs -0.1 (0.09); p=0.036 MADRS total score: -3.3 (0.46) vs -2.1 (0.47) vs -2.4 (0.61); p=0.209 Clinical response, % of group: 40.8 vs 40.3 vs 31.3%; p=0.063 No significant differences in time to response. Proportion of patients who reached remission, % of group: 42.8 vs 40.3 vs 35.4%; p=0.175	Aes, labs, ECGs, vital signs, and EPS (SAS, BAS, AIMS).

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Tohen, 2008 Multi-center: France, Germany, Lithuania, Puerto Rico, Romania, Russia, and U.S.	% of group, olanzapine (N=215) vs divalproex (N=201) vs placebo (N=105); p-value comparing olanzapine vs placebo: Dry mouth: 5.6 vs 2.5 vs 2.9%; p=0.224 Nausea: 0.9 vs 8.5 vs 2.9%; p=0.173 Weight increase: 8.8 vs 4.0 vs 2.9%; p=0.049 Increased appetite: 5.6 vs 5.5 vs 1.9%; p=0.110 Somnolence: 8.8 vs 2.5 vs 2.9%; p=0.045 Sedation: 5.6 vs 3.5 vs 4.8%; p=0.849 Headache: 4.2 vs 9.0 vs 8.6%; p=0.114 Insomnia: 0.9 vs 5.5 vs 3.8%; p=0.116 >=7% Weight gain: 6.4 vs 2.7 vs 1.0%; p=0.056 Mean (SD) change in prolactin (microg/L), baseline to Week 3: 6.5 (20.8) vs -5.7 (22.3) vs -1.8 (23.6); p<0.001 Significantly greater proportions of olanzapine-treated patients had fasting glucose and cholesterol increase to high levels. EPS: no treatment differences. Serious AEs in olanzapine during acute and 9-week continuation phase, N of patients: mania 2 suicidal ideation 2 bipolar I disorder 1 ectopic pregancy 1 pneumonia 1	Olanzapine (N=215) vs Divalproex (N=201) vs placebo (N=105): Total withdrawals: 26% vs 24.9% vs 26.7% Withdrawals due to AE: 7.4% vs 3.0% vs 1.0%	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Vieta 2008 Spain?	DB RCT Multicenter	18 years or older with DSM-IV criteria for bipolar I disorder, manic or mixed type (with or without psychotic features); diagnosis was confirmed by the Mini International Neuropsychiatric Interview, a history of at least one previous manic or mixed episode that required hospitalization and/or treatment with a mood stabilizer or antipsychotic.	Adjunctive aripiprazole (15 mg/day) or adjunctive placebo during the 6-week RCT	Phase 1 was a screening period (3–28 days, with an extension to 42 days with permission) during which medications other than lithium or valproate were discontinued and Phase 2 was a 2-week baseline period during which patients continued to receive open-label lithium or valproate monotherapy and confirmed partial nonresponse
Vieta 2008 Multinational International trial 126	DB RCT Multicenter (177)	At least 18 years, diagnosis of bipolar I disorder with at least one mixed episode, mania, or depression in the 2 years prior to the study, with an acute mixed episode, mania, or depression at enrollment, or a past mixed episode, mania, or depression within 26 weeks	Quetiapine (400–800 mg/day) plus lithium/divalproex or placebo plus lithium/divalproex for up to 104 weeks.	open-label quetiapine (400–800 mg/day; flexible, divided doses) with lithium or divalproex for up to 36 weeks to achieve at least 12 weeks of clinical stability

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Vieta 2008 Spain?	benzodiazepines (≤2 mg/day of lorazepam or equivalents) for a maximum of 10 days during the first 4 weeks only. Anticholinergic therapy (benztropine mesylate or equivalents, ≤2 mg/day) and propranolol (maximum dose of 20 mg t.i.d..., not to be taken within 8 hours of efficacy or safety assessment) were permitted for extrapyramidal symptoms. Propranolol for the treatment of heart disease was also permitted among those patients receiving it prior to enrollment.	YMRS, CGI-BP, MADRS and PANSS. During RCT assessments at day 4 and thereafter at weekly intervals until week 6.	Age 42 yrs % male 46 % white 91 % black 8 % other 1
Vieta 2008 Multinational International trial 126	previous medications for medical nonpsychiatric illnesses, but no psychoactive medications (other than the active treatments) were permitted phase prior to randomization and during randomized treatment, with the following exceptions, which were permitted throughout the study: low doses of zolpidem (up to 10 mg/day), zaleplon (up to 20 mg/day), zopiclone (up to 7.5 mg/day), and chloral hydrate (up to 1 g/day) for insomnia; the anxiolytic lorazepam (up to 2 mg/day); and anticholinergic medications for extrapyramidal symptoms	Time to recurrence via YMRS, MADRS, and Clinical Global Impression—Bipolar also used PANSS, Sheehans Disability Index (SDI) and Psychological General Well-being Scale (PGWB) for QOL	Age 42.1(12.7) years % male 45 % white 96.6 % black 1.6 % Asian 0.4 % Other 1.4

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Vieta 2008 Spain?	YMRS 23.1 Lithium 41% Valproate 59%	NR/NR/623	During RCT 74/5/377
Vieta 2008 Multinational International trial 126	Rapid cyclers 23.9% YMRS 2.4 (2.9) MADRS .5 (3.7)	NR/NR/1461 and 706 randomized after stabilization	347 (123 quetiapine and 233 placebo) /11/ 703 analyzed

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Vieta 2008 Spain?	Aripiprazole vs. placebo - changes from baseline YMRS –13.3 [SD=7.9] vs.. –10.7 [SD=7.6]; , P < 0.01 CGI-BP -1.9 (1.3) vs. -1.6 (1.2) P < 0.05 MADRS -2.3 (7.0) vs. -1.1 (7.3) P = 0.177 PANSS -4.1 (3.8) vs. -2.9 (3.7) P < 0.01 PANSS cognitive -3.1 (3.5) vs -2.0 (3.2) P < 0.01 PANSS hostility -3.0 (2.5) vs. -2.1 (2.6) P < 0.01	Reports of adverse events, vital signs, electrocardiogram (ECG) findings, and weight and laboratory assessments. Severity of extrapyramidal symptoms was assessed using the Simpson-Angus Scale, the Barnes Rating Scale for Drug-Induced Akathisia, and the Abnormal Involuntary Movement Scale (AIMS).
Vieta 2008 Multinational International trial 126	Estimated difference (SE) [95% CI] between QTP+Li/DVP (n=336) versus PBO+Li/DVP (n=367) YMRS −0.9 (0.2) [−1.2 to −0.6] P < 0.001 MADRS −0.7 (0.2) [−1.1 to −0.4] P < 0.001 CGI-BP −0.1 (0) [−0.2 to −0.1] P < 0.001 PANSS-P −0.2 (0.1) [−0.4 to −0.1] P < 0.001 SDS (observed cases data) −0.7 (0.4) [−1.5 to 0.2] P = 0.1149 PGWB 1.9 (0.8) [0.3 to 3.6] P = 0.0218 QTP+Li/DVP versus PBO+Li/DVP, the HR for the time to recurrence of a mood event was 0.28 (95% CI: 0.21–0.37; Pb0.001), corresponding to a risk reduction of 72%.	Used MedRA to classify The Simpson–Angus Scale (SAS) to evaluate EPS, akathisia via Barnes Akathisia Rating Scale (BARS) and Abnormal Involuntary Movement Scale (AIMS).

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Vieta 2008 Spain?	Placebo vs. aripiprazole Any 70 (53.8) vs 157 (62.1) P = 0.140 Akathisia 7 (5.4) vs. 47 (18.6) P = 0.001 Tremor 8 (6.2) vs. 23 (9.1) P = 0.349 Nausea 6 (4.6) vs. 21 (8.3) P = 0.175 Insomnia 5 (3.8) vs. 20 (7.9) P = 0.134 Headache 8 (6.2) vs 14 (5.5) P = 0.816 Diarrhea 7 (5.4) vs 11 (4.3)_ P = 0.666	Total withdrawals 74 30 due to AEs	
Vieta 2008 Multinational International trial 126	QTP+Li/DVP (n=336) vs.. PBO+Li/DVP (n=367) n (%) Somnolence 19 (5.7) vs. 8 (2.2) Nasopharyngitis 18 (5.4) vs. 20 (5.4) Headache 17 (5.1)vs. 21 (5.7) Insomnia 13 (3.9) vs. 52 (14.2)	347 withdrawals 17 (8 quetiapine and 9 placebo) due to AEs	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Vieta, 2007 (Companion to Calabrese 2005 BOLDER I) USA	Sub analysis of DB RCT Multicenter	18 to 65 years; DSM IV diagnosis of bipolar 1 or II disorder; current moderate to severe episode of major depression: HAM-D 17 ≥20; a HAM-D item 1 score ≥2 and a Young Mania Rating Scale (YMRS) score ≤12. Female patients of child-bearing potential were required to have a negative pregnancy test and to use adequate contraception. Exclusion - a diagnosis of an Axis I disorder other than BD in the 6 months prior and a current episode of depression of more than 12 months or less than 4 weeks in duration; DSM-IV diagnosis of dependence for any substance except nicotine within 12 months prior or a positive urine toxicology screen for illegal substances; a history of clinically significant cardiac, renal, neurologic, metabolic or pulmonary disease.	Quetiapine 600 mg/day, quetiapine 300 mg/day or placebo for 8 weeks	7-28 washout
Yatham, 2003 International	RCT Multicenter Hospitalized ≥ 4 days	Patients, aged 18-65, with DSM-IV bipolar disorder with a manic or mixed episode, minimum baseline score of 20 on the YMRS; receiving a mood stabilizer for a minimum of 2 weeks prior to screening; medically stable, randomized within 7 days of hospital admission	Adjunctive Risperidone 1-6 mg Placebo 3-week DB 10-week open-label	3-day washout

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Vieta, 2007 (Companion to Calabrese 2005 BOLDER I) USA	Medications for medical, non-psychiatric illnesses. First 3 weeks of the study, zolpidem tartrate (5–10 mg/day) at bedtime for insomnia and/or lorazepam (1–3 mg/day) for severe anxiety.	Mean change from baseline to week 8 in the Montgomery–Asberg Depression Rating Scale; protocol-defined response (≥50% reduction in MADRS score from baseline to week 8) and individual MADRS item scores; HAM-D; HAM-A; CGI-S and CGI-!. Assessments at days 1, 8, 15, 22, 29, 36, 43, 50, and 57.	Mean age 35.5 years 54% male 86% white 12% black 2% other
Yatham, 2003 International	Primary therapy with lithium, divalproex or carbamazepine Lorazepam 6 mg for agitation during the wash-out period and up to 4 mg daily during the first 7 days of the double-blind period Anti-parkinsonian and antidepressant drugs allowed after randomization	▪ Change in YMRS ▪ percent of patients showing a ≥ 50% improvement in YMRS score ▪ time (days) to onset of therapeutic response (≥ 30% improvement in YMRS score) ▪ change in CGI, BPRS, HRSD scores ▪ percent of patients who used adjunctive lorazepam	Mean age=39.5 58% female Ethnicity nr

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Vieta, 2007 (Companion to Calabrese 2005 BOLDER I) USA	62% Bipolar ! 38% Bipolar II	838/542/119	48/11/108 for efficacy
Yatham, 2003 International	Axis I diagnosis Bipolar disorder, manic=92% Bipolar disorder, mixed=8% Current episode Mild severity=3% Moderate severity=32.7% Severe with psychotic features=43.3% Severe without psychotic features=20.7%	NR/157/151 Risperidone n=75 Placebo n=76	66 (44%) withdrawn/2% lost to fu/142 (94.6%) analyzed

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Vieta, 2007 (Companion to Calabrese 2005 BOLDER I) USA	Quetiapine 600 mg/day and quetiapine 300 mg/day vs. placebo Change in mean MADRS from baseline −21.1 and −20.7 versus −11.6; p < 0.001 for each comparison change in mean HAM-D from baseline −17.4 and −16.3 versus −9.8, p < 0.001 for each quetiapine dose versus placebo change in mean HAM-A from baseline −12.4 (P < 0.001) and −10.5 (P = 0.006) versus −6.2	MedDRA classification system; Simpson-Angus Scale; Barnes Akathisia Rating Scale Treatment-emergent mania was defined as a YMRS score ≥16 on 2 consecutive study visits, at final visit, or when mania or hypomania was reported as an adverse event. Vital signs, 12-lead electrocardiograms (ECGs) and routine hematology and laboratory analyses conducted at baseline and week 8.
Yatham, 2003 International	Risperidone vs placebo YMRS Change in mean points: -49% vs -36%; p=NS % patients with ≥ 50% improvement: 59% vs 41%; p<0.05 Adjunctive lorazepam use (% patients): 72% vs 63%; p=NS CGI (% patients with 'much' or 'very much' improvement at endpoint): 61% vs 43%; p=0.022 BPRS (change in mean points): -10.1% vs -4.8%; p=0.006 HRSD (change in mean points): risperidone=placebo (data nr)	ESRS and CGI of overall severity of dystonia, parkinsonism and dyskinesia administered at baseline and on days 8, 15, and 22

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Vieta, 2007 (Companion to Calabrese 2005 BOLDER I) USA	Quetiapine 600 mg/day and quetiapine 300 mg/day vs. placebo (%) Dry mouth 42.4 and 48.9 vs. 0 Sedation 30.3 and 29.8 vs. 7.9 Dizziness 24.2 and 21.3 vs. 13.2 Constipation 21.2 and 12.8 vs. 2.6 Fatigue 21.2 and 8.5 vs 5.3 Somnolence 21.2 and 25.5 vs. 7.9 Nasal congestion 12.1 and 4.3 vs. 2.6 Blurred vision 12.1 and 4.9 vs. 2.6	Total withdrawals- 48 (40%) Due to AEs - 18 (15%)	
Yatham, 2003 International	Risperidone (n=75) vs placebo (n=75) % patients with ≥ 1 adverse event: 57% vs 51%; p=NS Extrapyramidal-related adverse events Any extrapyramidal-related adverse events: 21% vs 8%; p=0.013 Change in mean ESRS scores: -0.1 vs -0.1; p=NS Hyperkinesia: 7% vs 0; p=NS Tremor: 5% vs 1%; p=NS Extrapyramidal disorder: 4% vs 4%; p=NS Hypertonia: 4% vs 3%; p=NS Gait abnormality: 3% vs 0; p=NS Tetany: 3% vs 0; p=NS Ataxia: 1% vs 0; p=NS Dystonia: 1% vs 0; p=NS Hypokinesia: 1% vs 0; p=NS Dyskinesia: 0 vs 1%; p=NS Other Headache: 9% vs 9%; p=NS Insomnia: 4% vs 8%; p=NS Nausea: 5% vs 3%; p=NS Mean weight increase (kg): 1.7 vs 0.5; p=0.012	Risperidone (n=75) vs placebo (n=75) Total withdrawals: 36% vs 52%; p=NS Withdrawals due to adverse events: 1% vs 4%; p=NS	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Yatham, 2004 International	RCT, DB	Male and female hospitalized patients (>18 years) with a DSM-IV diagnosis of bipolar I disorder, whose most recent episode was manic and who had at least one manic or mixed episode in the previous 5 years, were eligible candidates for study. Pts had to have a YMRS score of > 20, including a score of > 4 on two of the core YMRS items of Irritability, Speech, Content, and Disruptive/Aggressive Behavior, and a Clinical Global Impression--Bipolar (CGI-BP) Severity of Illness score of > 4 (moderately ill).	Randomized to 3 or 6 weeks of (n=197) Quetiapine (QTP) with Lithium (Li) or Divalproex (DVP), or (n=205) placebo with Li/DVP. Quetiapine or placebo twice daily 100 mg/d up to 800 mg/d at end of study. Lorazepam 4 mg/d dose to 1mg/d at end of study.	Patients taking lithium or divalproex for >7 days,
Yatham, 2007 Belgium, Bulgaria, Canada, Germany, India, Rumania, South Africa, Spain and the UK	Multicentre, double-blind, randomized, parallel-group, placebo-controlled study Inpatient then after 1 week outpatient if deemed suitable	18 years or more; BP I disorder who had been hospitalized for an acute manic episode, and who had received treatment with a mood-stabilizing agent (Li or DVP) for => 7 days of the 28 days immediately before; at least one documented manic or mixed episode before and a YMRS score >= 20; with a score of => 4 on two of the four core YMRS items; score => 4 on the Clinical Global Impression-BP (CGI-BP) Severity of Illness scale Exclusion- see Sachs et al., 2004	Quetiapine (up to 800 mg/day) and lithium/divalproex (Li/DVP) or placebo and lithium/divalproex. 6 weeks	NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Yatham, 2004 International	1 sleeping aid per day- monitored,	Vital sign measurements performed at baseline and days: 4, 7, 10, 14,21. Tests: CGI-BP Global Improvement Scale, CGI-BP Severity of Illness PANSS Supplemental Aggression	Mean age; 39.9 years Male 47% Ethnicity NR
Yatham, 2007 Belgium, Bulgaria, Canada, Germany, India, Rumania, South Africa, Spain and the UK	Lorazepam was allowed for the first 10 days and previously prescribed medications for stable medical conditions were permitted throughout	YMRS, CGI, MADRS Assessed at baseline (day 1), and at days 4, 7, 10, 14, 21, 28, 35, and 42.	Mean age 39.5 years 50% male Ethnicity NR

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Yatham, 2004 International	Mean weight (kg): 79.9 Mean YMRS score: 31.9 Manic moderate (% patients): 30.5 Manic severe (% patients) Without psychotic features: 25.4 With psychotic features: 44.0	NR/NR/402	161 (40%) withdrawn 11 (3%) lost to follow up 230 analyzed
Yatham, 2007 Belgium, Bulgaria, Canada, Germany, India, Rumania, South Africa, Spain and the UK	Mean weight 73.5 kg Episode type (%) Manic moderate 27.0 Manic severe without psychotic features 27.5 Manic severe with psychotic features 45.5	250/211/211	78/7/209

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Yatham, 2004 International	Young Mania Rating Scale (YMRS) scores at Day 21: QTP + Li/DVP: -15.29 vs PBO + Li/DVP: -12.19 (P<0.05) Clinical Global Impression-Bipolar Severity of illness scores at Day 21: QTP + Li/DVP: -1.59 vs PBO + Li/DVP: -1.19 (P<0.01) CGI-BP Global Improvement Scale scores at Day 21: QTP + Li/DVP: 58.5% vs PBO + Li/DVP: 43.2% (P<0.01) PANSS Supplemental Aggression Risk Scores at Day 21: QTP + Li/DVP: -5.05 vs PBO + Li/DVP: -3.69 (P<0.05)	Patient self-report, medical examination.
Yatham, 2007 Belgium, Bulgaria, Canada, Germany, India, Rumania, South Africa, Spain and the UK	Quetiapine vs. placebo mean change YMRS total score – 17.1 vs. – 14.3 p = 0.17 YMRS response (%) 72.1 vs. 57.3 p = 0.03 YMRS remission (%) 68.3 vs. 57.3 p = 0.11 CGI Severity of Illness score – 1.9 vs. – 1.6 p = 0.18 CGI Global Improvement response (%) 76.0 vs. 59.4 p = 0.01 CGI-BP Severity of Illness score – 1.9 vs. – 1.6 p = 0.35 CGI-BP Global Improvement response (%) 74.0 vs. 58.3 p = 0.02	reports of adverse events, concomitant medication records, and changes from baseline to days 21 and 42 in clinical laboratory assessments, vital signs, electrocardiogram, physical examination and weight. COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) were used.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Yatham, 2004 International	Reported: QTP vs PBO Somnolence: 66 (33.7%) vs 19 (9.4%); P<0.001 Dry Mouth: 38 (19.4%) vs 6 (3.0%); P<0.001 Asthenia: 19 (9.7%) vs 8 (3.9%); P=0.034 Postural Hypotension: 13 (6.6%) vs 3 (1.5%); P=0.012 Weight Gain: 12 (6.1%) vs 5 (2.5%); P=0.090 Pharyngitis: 11 (5.6%) vs 5 (2.5%); P=0.134	QTP: 69 (35.2%) vs PBO: 92 (45.3%) Withdrawals due to adverse events: QTP: 7 (3.6%) vs PBO: 12 (5.9%)	
Yatham, 2007 Belgium, Bulgaria, Canada, Germany, India, Rumania, South Africa, Spain and the UK	Quetiapine vs. placebo (%) Somnolence 28.3 vs. 8.7 Dry mouth 19.8 vs. 1.9 Constipation 10.4 vs. 5.8 Weight gain 10.4 vs. 3.9 Serious AEs 1.9 vs. 6.8	Total withdrawals 78 due to AEs 8	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Young 2009 Multinational	DB RCT Multicenter	18 years or older with bipolar I disorder manic or mixed type (with or without psychotic features), as defined by DSM–IV10 and confirmed by the Mini International Neuropsychiatric Interview (MINI), who were experiencing an acute relapse requiring hospitalization	aripiprazole (15 or 30 mg/day; n=167) placebo (n=153) haloperidol (5–15 mg/day, n=165) 3 weeks and then placebo arm switched to aripiprazole for and additional 9 weeks	2-14 day washout

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Young 2009 Multinational	Benzodiazepines and anticholinergic therapy for the treatment of extrapyramidal symptoms and . Propranolol for the treatment of akathisia or tremor.	YMRS, CGI-BP, MADRS and PANSS and Longitudinal Interval Followup Evaluation – Range of Impaired Function Tool Assessed at baseline and at days 2, 4, 7 and 10 and thereafter at the end of weeks 2, 3, 4, 5, 6, 8, 10 and 12.	Mean age 41 years % male 44.3 % white 78 % black 16 % other 6

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Young 2009 Multinational	Baseline YMRS scores: placebo, 28.8; haloperidol, 28.0; aripiprazole, 28.4.	NR/NR/614	At 3 weeks 129/8/478 At 12 weeks 211/23/478

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Young 2009 Multinational	Placebo vs. Haloperidol vs. Aripiprazole 3 weeks Change in YMRS -9.7 vs.. -12.8 vs. -12.0 Placebo vs. Haloperidol P = 0.005, Placebo vs. Aripiprazole P = 0.039 CGI-BP -1.1 (0.1) vs -1.5 (0.1)** vs -1.4 (0.1)* MADRS -2.1 (0.4) vs -2.5 (0.4) vs -1.8 (0.4) PANSS total -4.7 (1.0) vs -8.8 (1.0)** vs -8.2 (1.0)* PANSS positive -2.4 (0.4) vs -4.2 (0.4)*** vs -3.8 (0.4) PANSS negative 0.1 (0.2) vs -0.3 (0.2) vs -0.4 (0.2) PANSS cognitive -1.5 (0.3) vs -2.5 (0.3)* vs -2.4 (0.3)* PANSS hostility -1.2 (0.3) vs -2.6 (0.3)*** vs -2.3 (0.3)** *P<0.05; **P<0.01; ***P<0.001 v. placebo Haloperidol vs. aripiprazole at 12 weeks Change in YMRS --17.8 vs. -17.2 P = 0.564 Placebo vs. Haloperidol P = 0.005, Placebo vs. Aripiprazole P = 0.039 CGI-BP -2.0 (0.1) vs -1.9 (0.1) MADRS -2.4 (0.5) vs -1.7 (0.5) PANSS total -11.7 (1.1) vs -9.8 (1.1) PANSS positive -5.4 (0.4) vs -4.9 (0.4) PANSS negative -0.3 (0.2) vs -0.2 (0.2) PANSS cognitive -3.9 (0.4) vs -3.2 (0.4) PANSS hostility -3.5 (0.3) vs -3.0 (0.3)	Vital sign measurements randomization, and then on a weekly basis until week 3 and at weeks 8 and 12. Routine laboratory tests and weight measurements at screening, baseline, week 3 and week 12. Adverse event reports were recorded at each assessment. Extrapyramidal symptoms were evaluated using the Simpson–Angus Scale (SAS), the Barnes Akathisia Rating Scale (BARS) and the Abnormal Involuntary Movement Scale (AIMS).

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Young 2009 Multinational	Weeks 1–3 Placebo vs. Haloperidol vs. Aripiprazole n (%) Akathisia 7 (4.6) vs 34 (20.6) vs. 15 (9.0) Extrapyramidal disorder 1 (0.7) vs. 20 (12.1) vs. 12 (7.2) Headache 12 (7.8) vs. 8 (4.8) vs. 11 (6.6) Insomnia 19 (12.4) vs. 10 (6.1) vs. 23 (13.9) Muscle rigidity 1 (0.7) vs. 13 (7.9) vs. 2 (1.2) Mania 11 (7.2) vs. 1 (0.6) vs. 8 (4.8) **Weeks 1–12 Haloperidol vs. Aripiprazole n (%)** Headache 12 (7.3) vs. 16 (9.6) Akathisia 41 (24.8) vs. 19 (11.4) Extrapyramidal disorder 25 (15.2) vs. 13 (7.8) Muscle rigidity 16 (9.7) vs. 2 (1.2) Tremor 12 (7.3) vs. 10 (6.0) Insomnia 10 (6.1) vs. 24 (14.5) Somnolence 8 (4.8) vs. 9 (5.4) Anxiety 5 (3.0) vs. 9 (5.4) Mania 2 (1.2) vs. 10 (6.0)	At 3 weeks total withdrawals 129, due to AEs 38 At 12 weeks 211 withdrawals, due to AEs 67	Baseline info and Adverse events came from online supplement at journal website.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Young, 2010 Europe, Canada, Asia EMBOLDEN I	DB RCT Multicenter (110 centers)	Inclusion: Adult outpatients (aged 18-65 years) meeting DSM-IV criteria for bipolar I or II disorder (with or without rapid cycling; ≥4 episodes/year to ≤8 per year) and who were experiencing a recent major depressive episode (duration ≤1 year and onset ≥4 weeks) prior to entry; HAM-D score ≥20 and an HAM-D item 1 (depressed mood) score ≥2 Exclusion: 1) active Axis I disorders requiring treatment within 6 months of study entry; 2) a YMRS total score ≥12; 3) a history of non-response to an adequate treatment period (6 weeks) with ≥2 classes of anti-depressants during the current episode; 4) known non-response to quetiapine or lithium, as judged by the investigator; 5) substance dependence (DSM-IV) or abuse; 6) a current serious suicidal or homicidal risk (as judged by the investigator); and 7) a clinically relevant medical illness	Quetiapine 300 mg/day vs quetiapine 600 mg/day vs placebo vs lithium 600 to 1800 mg/day 8 weeks	Washout period of at least 5 to 28 days, during which prior psychotropic medications were discontinued
Zimbroff, 2007 USA	RCT NR	Included were voluntarily hospitalized patients aged 18 years or older who were experiencing acute agitation (Positive and Negative Syndrome Scale [PANSS] Excited Component [PEC] score of 15–32, with a score of 4 or more [moderate] on 2 or more of the 5 PEC items [hostility, lack of cooperation, excitement, poor impulse control, and tension]) and had a diagnosis of bipolar I disorder, manic or mixed episode. Exclusion criteria included a diagnosis of schizophrenia, schizoaffective disorder, delirium, dementia, and amnestic or other cognitive disorders; a psychiatric diagnosis other than bipolar I disorder requiring pharmacotherapy; patients experiencing their first manic episode; nonresponders to prior antipsychotic agents; significant medical history exposing patients to undue risk of significant adverse events (AEs) or interfering with safety/efficacy assessments.	IM aripiprazole 9.75 mg per injection (1.3 mL of a 7.5-mg/mL solution to approximate a dose of 10 mg), IM aripiprazole 15 mg per injection (2.0 mL of a 7.5-mg/mL solution), IM lorazepam 2 mg per injection (1 mL of a 2-mg/mL solution), or IM placebo after a 2-hour or more screening period. 3 injections allowed within 24 hours.	None

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Young, 2010 Europe, Canada, Asia EMBOLDEN I	Continuation of nonpsychotropic medications taken prior to study entry was permitted. Lorazepam (1-3 mg/day for severe anxiety) and hypnotics (zolpidem tartrate up to 10 mg/day, zaleplon up to 20 mg/day, zopiclone up to 7.5 mg/day, or chloral hydrate up to 1 mg/day at bedtime for insomnia) were allowed during the first 3 weeks of treatment at the investigator's discretion.	MADRS; CGI - severity of illness and change; HAM-D; HAS; Sheehan Disability Scale; Assessments performed at baseline, at weeks 1 and 2, and then every 2 weeks until week 8 Medical Outcomes Study Cognitive Scale; Assessments performed at baseline, week 4 and week 8.	Mean age: 42.2 years 40.7% male Ethnicity: NR
Zimbroff, 2007 USA	Use of benztropine or a similar anticholinergic agent (6 mg/d benztropine or equivalent) was permitted after the first injection to treat EPS Zolpidem or zaleplon (10 mg/d) can be given to aid sleep 1 hour or more after the second/third injection.	PEC score from baseline at 2 hours (LOCF analysis). Secondary measures included Clinical Global Impression (CGI)–Improvement (CGI-I) and CGI–Severity of Illness (CGI-S) scales, Agitation–Calmness Evaluation Scale (ACES), Corrigan Agitated Behavior Scale (CABS), Young Mania Rating Scale (YMRS), and response rate (40%reduction in PEC score from baseline at 2 hours)	Mean age 40.8 years, 52% male 72% white

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Young, 2010 Europe, Canada, Asia EMBOLDEN I	Quetiapine 300 mg/day vs Quetiapine 600 mg/day vs placebo vs lithium Bipolar disorder type I: 62.7% vs 61.6% vs 60.5% vs 64% Bipolar disorder type II: 37.3% vs 38.4% vs 39.5% vs 36% Mean MADRS total score: 28.1 vs 28.3 vs 28.5% vs 28.3 Mean HAM-D total score: 24.2 vs 24.3 vs 24.4 vs 24.1 Mean YMRS total score: 3.1 vs 3.3 vs 3.3 vs 3.4 Mean HAS total score: 18.3 vs 18.2 vs 18.3 vs 18 Mean CGI-S total score: 4.4 vs 4.3 vs 4.3 vs 4.4	1042/NR/802	199/4/783
Zimbroff, 2007 USA	Mean scale scores: CGI-S=4.1 ACES=2.4 CABS=28.7 YMRS=23.7 SAS=11.3 BARS=0.7	NR/NR/301	19/10/291

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Young, 2010 Europe, Canada, Asia EMBOLDEN I	Quetiapine 300 mg/day vs Quetiapine 600 mg/day vs placebo vs lithium *P* value is versus placebo Mean change MADRS (SE): -15.36 (0.93); *P* <0.001 vs -16.1 (0.92); *P* <0.001 vs -11.81 (1.1) vs -13.6 (1.08); *P* =0.123 Mean change in HAM-D (SE): -13.98 (0.78); *P* <0.001 vs -14.17 (0.77); *P* <0.001 vs -10.72 (0.91) vs -12.36 (0.9); *P* =0.082 Mean change in HAM-D item 1 - depressed mood (SE): -1.52 (0.1); *P* =0.023 vs -1.62 (0.1); *P* =0.001 vs -1.26 (0.12) vs -1.36 (0.12); *P* =0.438 Mean change in CGI-S (SE): -1.51 (0.13); *P* =0.008 vs -1.57 (0.13); *P* =0.002 vs -1.14 (0.15) vs -1.4 (0.15); *P* =0.98 Mean change in HAS (SE): -9.14 (0.63); *P* <0.001 vs -9.29 (0.63); *P* <0.001 vs -6.55 (0.75) vs -7.72 (0.74); *P* =0.144	Incidence and severity of AEs; withdrawals due to AEs; EPS (SAR-S and BARS); laboratory tests, weight and body mass index, ECG, physical examination, and vital signs; treatment emergent mania or hypomania (YMRS total score ≥16 on 2 consecutive assessments or at final assessment, or an AE report of treatment-emergent or hypomania); treatment-emergent suicidal ideation (HAM-D item 3 score ≥3 or an AE of suicidality, suicidal ideation, suicide attempts, or suicide completion)
Zimbroff, 2007 USA	IM Placebo vs.IM Aripiprazole 9.75 mg vs. IM Aripiprazole 15 mg vs. IM Lorazepam CGI-I at 2 hours 3.1 vs. 2.2* vs. 2.3* vs. 2.1* CGI-S Change at 2 hours 0.9 vs. 1.5* vs. 1.3y vs. 1.6* ACES Change at 2 hours +1.0 vs. +1.9* vs.+2.3* vs. +2.3* CABS Change at 2 hours 6.4 vs. 9.6* vs. 9.1* vs. 10.4* YMRS Change at 2 hours 7.0 vs. 11.4y vs. 10.6y vs. 10.8y PEC response rate at 2 hours (%) 37 vs. 69* vs. 63* vs. 69* SAS n = 71 n = 75 n = 73 n = 69 Change at 24 hours 0.5 vs. 0.6 vs. 0.3 vs. 0.5 BARS n = 71 n = 75 n = 74 n = 69 Change at 24 hours 0.4 vs. 0.4 vs. 0.3 vs. 0.4 *P ≤ 0.01 vs placebo. yP ≤ 0.05 vs placebo.	Patient reported and extrapyramidal symptoms were evaluated using the Simpson-Angus Scale (SAS) and the Barnes Akathisia Rating Scale (BARS) at baseline, 2, 4, 6, 12, and 24 hours, and before repeat injections. Lab tests were performed at baseline and at 24 hours. Vital signs (standing and supine blood pressures) were assessed at baseline, 1, 2, 4, 6, 12, and 24 hours, and 0.5 and 1 hour after repeat injections. Continuous ambulatory 12-lead ECG monitoring (from 2 to 22 hours) tracings were evaluated at 0.5, 1, 1.5, 2, 3, 4, 6, and 12 hours, and 0.5 and 1 hour after repeat injections. Standard 12-lead ECG was performed at 1 and 24 hours, and 1 hour after repeat injections.

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comment
Young, 2010 Europe, Canada, Asia EMBOLDEN I	Quetiapine 300 mg/day vs Quetiapine 600 mg/day vs placebo vs lithium Serious AEs: 3.8% vs 2.6% vs 2.3% vs 2.2% Treatment-emergent mania: 4.2% vs 2.2% vs 0.8% vs 2.2% Treatment-emergent suicidal ideation: 1.9% vs 1.1% vs 2.3% vs 0.7% EPS-related AEs: 5% vs 7.5% vs 3.8% vs 8.1% Mean change in SAR-S: -0.1 vs 0 vs -0.2 vs -0.1 Mean change in BARS: 0 vs 0 vs -0.1 vs 0 Somnolence: 18.1% vs 17.6% vs 8.8% vs 3.8% Dry mouth: 14.2% vs 15% vs 7.4% vs 1.5% Dizziness: 9.6% vs 11.2% vs 4.4% vs 5.3% Headache: 7.3% vs 8.6% vs 9.6% vs 13.7% Sedation: 6.2% vs 5.2% vs 0.7% vs 1.5% Constipation: 4.6% vs 7.9% vs 2.9% vs 2.3% Nausea: 3.8% vs 5.6% vs 16.9% vs 7.6% Diarrhea: 2.3% vs 2.6% vs 6.6% vs 3.8% Insomnia: 2.3% vs 1.1% vs 8.8% vs 5.3% Tremor: 0.8% vs 3.4% vs 5.9% vs 0.8% Weight change (SE): 0.6 (0.17) vs 0.8 (0.17) vs -0.7 (0.23) vs 0.2 (0.19) kg Prolactin change (SE): -4.12 (2.38) vs -3.87 (1.95) vs -7.7 (2.66) vs -0.82 (2.56) µg/L	Quetiapine 300 mg/day vs Quetiapine 600 mg/day vs placebo vs lithium Total withdrawals: 65 vs 63 vs 37 vs 34 Withdrawals due to AEs: 26 vs 35 vs 11 vs 12	
Zimbroff, 2007 USA	IM Placebo vs.IM Aripiprazole 9.75 mg vs. IM Aripiprazole 15 mg vs. IM Lorazepam Headache 9 (12.5) vs. 11 (14.7) vs.13 (17.3) vs.3 (4.4) Insomnia 6 (8.3) vs. 8 (10.7) vs. 5 (6.7) vs. 1 (1.5) Dizziness 4 (5.6) vs. 2 (2.7) vs. 9 (12.0) vs. 7 (10.1) Nausea 4 (5.6) vs. 8 (10.7) vs. 14 (18.7) vs. 0 Somnolence 4 (5.6) vs. 6 (8.0) vs. 6 (8.0) vs. 5 (7.3) Sedation 1 (1.4) vs. 3 (4.0) vs. 4 (5.3) vs. 8 (11.6) Vomiting 1 (1.4) vs. 3 (4.0) vs. 5 (6.7) vs. 0	19 withdrawals 2 due to AE	

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Altamura, 2003	NR	NR	Yes	Yes	Unclear	No	No
Amsterdam, 2005	Method not described	NR	No; differences in illness duration among the arms (range 15-24 years) and episode duration (12-30 months)	Yes	Unclear, reported as DB	Unclear, reported as DB	Unclear, reported as DB
AZ-D144CC00004	Method not described	Method not described	Yes	Yes	Stated as double-blind	Stated as double-blind	Yes
AZ-D1447C00144	Method not described	Method not described	Yes	Yes	Stated as double-blind	Stated as double-blind	Yes
Brecher, 2003 Poster	NR	NR	Yes	Yes	Yes	Yes	Yes
Brown 2008	NR	NR	Mostly, quetiapine group had more white participants than the placebo group and YMRS scores were higher in the placebo group	Yes	NR	Stated as double-blind	Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Quality rating	Comments
Altamura, 2003	NR, NR, NR, NR	NR NR	Unclear		Poor	
Amsterdam, 2005	Yes, NR, NR, NR	~41% discontinued before end of trial Differential: NR	NR; preliminary efficacy analyses were descriptive; did not specify which population they used for their analyses and how missing data were to be handled		Poor	Is 8 weeks long enough time to assess whether fluoxetine doesn't induce mania?
AZ-D144CC00004	NR, NR, NR, NR	NR NR	No Not all randomized were evaluated. Reported 96.1% and 98.8% in efficacy ITT	NR	Fair	
AZ-D1447C00144	Yes, NR, NR, Yes	NR NR	No 1172/1226 (95.6%) included	NR	Fair	
Brecher, 2003 Poster	Yes, NR, NR, NR	No No	LOCF		Fair	
Brown 2008	Yes, No, No, No	No No	Yes; only (13; 11%) excluded participants from analysis without a postbaseline assessment		Fair	

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

	Internal validity						
Author, year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Calabrese, 2004 Poster	NR	NR	Yes	Yes	Yes	Yes	Yes
Cutler; Ortho - NCT00299715-2007	NR	NR	Sample characteristics NR	Yes	NR	Stated as double-blind	Yes
Harvey, 2007	Method not described	NR	Yes	Yes	Unclear, reported as DB	Unclear, reported as DB	Unclear, reported as DB
Hirschfeld, 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Quality rating	Comments
Calabrese, 2004 Poster	Yes, NR, NR, NR	NR NR	LOCF		Fair	
Cutler; Ortho - NCT00299715-2007	Partially: reported attrition due to AEs No No No	No No	Yes; 2 (0.4%) subjects excluded from efficacy analysis	NR	Fair	
Harvey, 2007	Yes, Yes, Adherence-subjects stayed at the testing site to ensure compliance, NR	~7% (2/30) withdrew Differential: low	No, but 93% completed the study		Fair	Evaluating cognitive fxn is important but this study did not evaluate the long-term effects. The duration of the study needs to longer in order to adequately assess whether these drugs truly have an adverse effect on long-term cognition.
Hirschfeld, 2004	Yes, NR, NR, NR	No No	No; 12 (4.6%) excluded from endpoint analysis; 3 because they didn't have "at least two efficacy assessments", and 9 from one site due to GCP noncompliance or protocol violations ("repeat patients"); no mention of results from "worst case scenario" sensitivity analysis that included those 12 patients; data on file, submitted 11/9/04 was included in this consideration		Fair	

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Houston, 2009	NR	NR	Yes	Yes	Stated as DB	Stated as DB	Stated as DB
Keck 2009	NR	NR	Mostly; placebo group had more white participants	Yes	NR	Stated as double-blind	Stated as double-blind
Keck, 2003	NR	NR	Yes	Yes	Yes	Yes	Yes
Keck, 2006	Method not described	NR	No; more males were randomized to aripiprazole than placebo; more patients with mania randomized to placebo arm and more subjects with mixed-type BPAD randomized to aripiprazole arm	Yes	Unclear reported as DB. Note: 'experienced raters' administered efficacy scales and effort was made to ensure that same raters were used but the authors did not specify whether they were blinded to treatment allocation	Unclear, reported as DB	Unclear, reported as DB
Khanna, 2003	NR	NR	Yes	Yes	Yes	Yes	Yes
Kwentus; Ortho NCT00309699-2007	NR	NR	Sample characteristics NR	Yes	NR	Stated as double-blind	Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Quality rating	Comments
Houston, 2009	Yes, No, No, No	No, No	NR Reported ITT was conducted but data to support ITTY not provided	Yes	Fair	
Keck 2009	Yes, No, No, No	No; No	Yes; only people (8) excluded from analysis were those without a postbaseline assessment		Fair	
Keck, 2003	Yes, NR, NR, NR	NR NR	No		Fair	
Keck, 2006	Yes, NR, NR, NR	58.4% withdrew Differential: ~16% difference between placebo and aripiprazole arm	Yes		Fair	
Khanna, 2003	Yes, NR, NR, NR	No No	LOCF		Fair	
Kwentus; Ortho NCT00309699-2007	Yes No No No	No No	Yes; analyses only excluded 2 (0.4%) patients who discontinued before receiving study medication	NR	Fair	

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Macfadden 2009	NR	NR	No RLAT group older at 1st diagnosis of bipolar I	Yes	Yes for relapse (independent relapse monitoring board)	Stated as double-blind	Yes
McElroy 2010 (EMBOLDEN II)	NR	Yes	Yes	Yes	Yes	Yes	Yes
McIntyre 2009 3-week	Method not described	NR	No MADRS, ALT,AST,CK higher in placebo group	Yes	Stated as double-blind	Stated as double-blind	Yes
McIntyre 2009 Asenapine vs. olanzapine	Method not described	NR	Yes	Yes	Stated as double- blind	Stated as double-blind	Stated as double-blind
McIntyre 2009	NR	NR	Yes Very little comparison data provided	Yes	Stated as double-blind	Stated as double-blind	Yes
Morozova; Ortho NCT00132678-2007	NR	NR	NR between treatment groups	Yes	NR	Stated as double-blind	Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Quality rating	Comments
Macfadden 2009	Yes, No, Yes, No	No No	No Patients with > 1 dose study medication included. Data not reported	NR	271 (240 enrolled in stabilization phase)/183/124	
McElroy 2010 (EMBOLDEN II)	Yes, No, No, No	No, Yes (36%)	Yes, 95% included in analysis using LOCF	Yes	Fair	
McIntyre 2009 3-week	Yes, No, No, No	No No	No 480 /489 (98%) included	Yes	Fair	
McIntyre 2009 Asenapine vs. olanzapine	Yes, No, No, No	No No	No 491/504 (97%) included	Yes	Fair	
McIntyre 2009	Yes, No, No, No	No No	No 480/489 (98.2%) included	Yes	654/NR/489	
Morozova; Ortho NCT00132678-2007	Partially: reported attrition due to AEs No No No	No NR	No; excluded 9.2% of subjects from efficacy analysis	NR	Fair	Excluded 28 of 303 from efficacy analysis, reasons not stated. All 303 included in safety analysis.

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Muzina 2008	NR	NR	Mostly, placebo group had more white participants	Yes	NR	Stated as double-blind	Yes
Nejtek 2008	Assigned in blocks of 10	No	Yes	Yes	Yes	Yes	Yes
Nierenberg, 2006	No. Equipoise randomization - considering which options were acceptable to patient. 3 subjects included in more than one group.	NR	Some differences; Bipolar I range 16.7% to 68.8%, Bipolar II range 31.2% to 83.3%.	Yes	No	No	No
Paulsson, 2003	NR	NR	Yes	Yes	Yes	Yes	Yes
Perlis, 2006	Unclear- "1:1 fashion"	NR	Yes	Yes	NR	NR	NR
Potkin, 2005	Yes	Yes	Some differences; >\# manic in Placebo, >\# mixed in ziprasidone groups	Yes	Yes	Yes	Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Quality rating	Comments
Muzina 2008	Yes, No, No, No	No No	Used a last observation cared forward approach		Fair	
Nejtek 2008	Yes No No No	31% lost to follow-up (32% in risperidone group and 31% in quetiapine group)	Yes		Fair	
Nierenberg, 2006	Yes NR NR NR	Unclear.	Yes; but 3 patients crossed over into more than one group and were accounted for twice in the analysis		Poor	
Paulsson, 2003	Yes NR NR NR	No No	No, 2 (0.6%) excluded for unspecified reasons		Fair	
Perlis, 2006	Yes NR NR NR	Yes reported; > in olanzapine group (21.3%) vs. risperidone group (33%) (p= 0.019) Differential, not high	Yes		Fair	
Potkin, 2005	Yes NR NR NR	41% discontinued study overall 39% ziprasidone 46% placebo	Yes; LOCF for missing data		Fair	

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Riesenberg; Ortho NCT00309686-2007	NR	NR	NR between treatment groups	Yes	NR	Stated as double-blind	Yes
Sachs, 2004	NR	NR	Yes	Yes	Yes	Yes	Yes
Sachs, 2005	NR	NR	Yes	Yes	NR	Yes	Yes
Schering-Plough 7501004	Yes	NR	Yes	Yes	Yes	Stated as double-blind	Yes
Schering-Plough 7501008	Yes	NR	Yes	Yes	Yes	Stated as double-blind	Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Quality rating	Comments
Riesenberg; Ortho NCT00309686-2007	Partially: reported attrition due to AEs No No No	No No	Yes; 1 subject (0.3%) did not receive the DB medication and was excluded from analysis	NR	Fair	
Sachs, 2004	Yes NR NR NR	No No	No, 21 (11%) were excluded (includes patients with no post baseline assessments and patients from one complete center due to protocol violations)		Fair	
Sachs, 2005	Yes NR Yes NR	NR NR	No, 4 (1.4%) patients excluded from efficacy analysis, and 3 (1.1%) patients excluded from safety analysis		Fair	
Schering-Plough 7501004	Yes No No No	No / No Completion rates (%) Asenapine v. placebo v. Olanzapine: 67 v. 58.2 v. 78.5	Stated to be. Analysis excluded 8 (1.6%) of 488 randomized	NR	Fair	
Schering-Plough 7501008	Yes No No No	High, not differential. Completion rates (%) Asenapine v. placebo: 38.4 v. 32.9	Stated to be. Analysis excluded 8 (2.5%) of 326 randomized.	NR	Fair	

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Sheehan 2009	NR	NR	No Risperidone gp higher proportion of mixed mood state & current depression and > patients with lifetime panic disorder, higher Simpson Angus Scale scores	Yes	Stated as double-blind	Stated as double-blind	Yes
Suppes 2009	NR	NR	Yes	Yes	NR	Stated as double-blind	Stated as double-blind
Suppes 2010	NR	NR	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind
Thase, 2006	Unclear; "interactive voice-response central randomization service"; 2:1 ratio for bipolar diagnosis, (1:1:1 for placebo, 300 mg or 600 mg groups).	Unclear	Yes	Yes	Unclear	Unclear	Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Quality rating	Comments
Sheehan 2009	Yes, No, No, No	No No	No 103/111 (92.8%) in ITT	Yes 9 with no post baseline data excluded from analysis	NR/NR/111	
Suppes 2009	Yes No No No	No No	Yes		Fair	
Suppes 2010	Yes, Yes, No, No	No Yes, 33%	Yes, 270 (96%) analyzed using LOCF	Yes	Fair	
Thase, 2006	Yes NR NR NR	Yes reported; Overall non-completion rates: 34.5% placebo, 41.3% in quetiapine 300mg group, 46.7% in quetiapine 600 mg group. Highest in 600 mg group.	Yes; stating using LOCF		Fair	

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

	Internal validity						
Author, year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Thase, 2008	Yes	NR	Yes	Yes	Yes	Yes	Yes
Tohen 2008	Yes	Yes	Yes	Yes	Unclear	Yes	Yes
Tohen 2008	Yes	Yes	Somewhat	Yes	NR	Stated as double-blind	Yes
Tohen, 1999	NR	NR	NR	Yes	Yes	Yes	Yes
Tohen, 2000	Yes	No; personnel at the site assigned a patient to the next available kit	Yes	Yes	Yes	Yes	Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Quality rating	Comments
Thase, 2008	Yes No No No	Discontinuations were high and differential in both Study 1 and 2 Study 1: aripiprazole=46.8% vs placebo=35.1% Study 2: aripiprazole=41.2% vs placebo=29.8%	Efficacy sample: Study 1: aripiprazole=164 (88.2%) vs placebo=177 (94.1%) Study 2: aripiprazole=176 (94.1%) vs placebo=178 (94.5%)		Fair	
Tohen 2008	Yes No No No	No No	Yes		Good	"Olanzapine versus divalproex versus placebo in the treatment of mild to moderate mania: a randomized, 12-week, double-blind study"
Tohen 2008	Yes No No No	No No	Yes		Fair	"Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes"
Tohen, 1999	Yes NR NR NR	NR NR	No, 3 (2.2%) patients excluded due to not having a post-baseline assessment		Fair	
Tohen, 2000	Yes NR NR NR	No No	No, 5 (4.3%) patients excluded due to not having a post-baseline assessment		Fair	

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Tohen, 2003	NR	Yes	No; Mean length of current depressive episode shorter for olanzapine group	Yes	Yes	Yes	Yes
Tohen, 2004	NR	Yes	Yes	Yes	Yes	Yes	Yes
Tohen, 2006	NR	NR	Yes for demographics, however randomization ratio of 2:1 in favor of olanzapine	Yes	NR	NR	Yes
Vieta 2008	NR	NR	Yes	Yes	Unclear	Stated as double-blind	Stated as double-blind

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Quality rating	Comments
Tohen, 2003	Yes NR NR NR	No No	No		Fair	
Tohen, 2004	Yes NR NR NR	NR NR	Yes		Fair	
Tohen, 2006	Yes NR Yes NR	Yes/7.1% open-label phase, 8.4% olanzapine double-blind phase, 3.7% placebo double-blind phase	Yes for both open-label and double-blind phase		Fair	
Vieta 2008	Yes No No No	No No	Unclear		Fair	"Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of patients with bipolar I disorder (international trial 126)"

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

	Internal validity						
Author, year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Vieta 2008	NR	NR	Yes	Yes	Unclear	Stated as double-blind	Stated as double-blind
Yatham, 2003 International	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yatham, 2007	NR; larger portion received Li vs DVP - investigators were asked to choose the appropriate med for each patient based on clinical history/condition	NR	Yes	Yes	NR	NR	Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Quality rating	Comments
Vieta 2008	Yes No No No	No No	Yes		Fair	"Efficacy of Adjunctive Aripiprazole to Either Valproate or Lithium in Bipolar Mania Patients Partially Nonresponsive to Valproate/Lithium Monotherapy: A Placebo-Controlled Study"
Yatham, 2003 International	Yes NR NR NR	No No	No; 10 (6.7%) excluded from endpoint analysis; 8 because they didn't have "at least two efficacy assessments", and reasons for other 2 not specified; no mention of results from "worst case scenario" sensitivity analysis that included those 10 patients; data on file, submitted 11/9/04 was included in this consideration		Fair	
Yatham, 2007	Yes NR NR NR	Yes reported; overall discontinuation rates: 39.8% placebo vs. 33% quetiapine group (significance not reported).	Yes		Fair [not sure how investigator choice of Li or DVP may change study results]	

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Internal validity

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Young 2009	NR	NR	Yes	Yes	NR	Stated as double-blind	Stated as double-blind
Young 2010	NR	Yes	Yes	Yes	Yes	Yes	Yes
Zimbroff 2007	NR	NR	Yes	Yes	Yes	Yes	Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Maintenance of comparable groups	Quality rating	Comments
Young 2009	Yes No No No	No No	Yes		Fair	
Young 2010	Yes, No, No, No	No, No	Yes; analysis included 783 (98%) using LOCF	Yes	Good	
Zimbroff 2007	Yes No No No	No No	Yes; analyses only excluded 10 (3%) patients who discontinued before receiving study medication		Fair	

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow up	Interventions Mean dose
Comparative studies					
Altamura, 2008	Observational trial at single center	Inclusion - either gender, age ranging between 22 and 79 years who had been diagnosed with DSM-IV Bipolar I (n=91) or Bipolar II Disorder (n=141), with or without comorbid Axis I disorders, and followed up at the Mood Disorder Unit of the Department of Psychiatry of the University of Milan between the years 2001 and 2005, and all euthymics at the time of the beginning of the study. Exclusion - psychotic disorders, mental retardation, serious cardiovascular or thyroid dysfunction, pregnancy, lactation, serious and unstable medical illness, any central nervous system or neuromuscular disorder, documented history of intolerance to mood stabilizers, and psychiatric disorders due to medical condition.	Follow up of 4 years Mean daily doses were: 214.0 mg/day (189.0 SD) for quetiapine monotherapy, 223.5 mg/day (147.2 SD) for quetiapine in combination with lithium, 215.2 mg/day (237.4 SD) for quetiapine in combination with sodium valproate, 79.2 mg/day (39.5 SD) for lamotrigine	NA	NR
Hassan, 2007 USA	Medicaid administrative claims database	Retrospective	January 1, 1999, to December 31, 2001	2 years	Risperidone, olanzapine, quetiapine, or typical antipsychotic

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Comparative studies				
Altamura, 2008	Scales assessed monthly by trained psychiatrists who administered the 21-item Hamilton Depression Rating Scale(HAMD-21) and the Young Mania Rating Scale (YMRS) Primary outcome measures were the duration of euthymia (i.e., survival time) from the beginning of the study and the cumulative proportion of subjects who maintained euthymia.	Mean age 52 yrs 35% male Ethnicity NR	BD I 39% BD II 61%	NR/NR/232
Hassan, 2007 USA	Under 65 years Medicaid recipients	NR NR NR	NR/832/825	NA/NA/825

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Effectiveness outcomes
Comparative studies	
Altamura, 2008	92/NR/232
Hassan, 2007 USA	Medication Possession Ratio = (total days supplied for index drug) / (total days from index to date of last prescription of index drug + days supplied for last fill) olanzapine 0.68 ±0.27 risperidone 0.68 ± 0.29 quetiapine 0.71 ± 0.25 typical antipsychotics 0.46 ± 0.34 Persistence - total days from the index prescription fill date until the occurrence of a filled prescription for any other index or nonindex antipsychotic or until discontinuation of therapy with the index drug. risperidone 194.8 ± 127.8 days olanzapine 200.9 ± 130.4 quetiapine 219.8 ± 128.9 days typical antipsychotic 179.2 ± 123.0 days for the cohort.

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Safety Outcomes	Comments
Comparative studies		
Altamura, 2008	quetiapine, vs. lithium vs. sodium valproate vs. lamotrigine, vs. quetiapine plus lithium, vs. quetiapine plus sodium valproate. Cumulative proportion of survival at 4 years 29.3% vs. 46.2% vs. 32.9% vs. 41.9% vs. 80% vs. 78.3% Mean survival time (months) 24.9 (2.7 s.e.) vs.33.1 (2.5 s.e..) vs. 26.3 (2.0 s.e..) vs. 30.1 (3.1 s.e..) vs. 41.4 (2.7 s.e..) vs. 39.2 (3.5 s.e..) Cumulative proportion of survival at 4 years from major depressive episodes 43.9% vs. 48.7% vs. 34.2% vs. 38.7% vs. 80% vs. 78.3% Mean survival time (months) from major depressive episodes 31.8 (2.6 s.e..) vs. 33.3 (2.5 s.e..) vs. 26.5 (2.0 s.e..) vs. 30.4 (2.8 s.e..) vs. 41.4 (2.7 s.e..) vs. 39.7 (3.3 s.e..) Cumulative proportion of survival at 4 years from manic episode 68.3% vs. 94.9% vs. 65.8% vs. 64.5% vs. 84% vs. 87% Mean survival time (months) from manic episodes 35.7 (2.8 s.e..) vs. 47.6 (0.3 s.e..) vs. 38.1 (1.8 s.e..) vs. 36.3 (3.0 s.e..) vs. 43.0 (2.3 s.e..) vs. 42.7 (2.9 s.e..)	NR
Hassan, 2007 USA	NR	

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow up	Interventions Mean dose
Gianfrancesco, 2007 United States	PharMetrics database; medical and prescription claims data	Retrospective	1999 through August 2003	NR	Risperidone 1.7mg, olanzapine 8.3mg, quetiapine 160mg, ziprasidone 70mg
Zhu, 2007 United States	PharMetrics Integrated Database for medical and pharmacy claims	Retrospective	January 2003 to December 2004	1 year	Olanzapine 11.0 ± 7.1 mg/day, quetiapine 192.6 ±183.1 mg/day risperidone 2.1 ± 1.7 mg/day, ziprasidone 101.2 ± 60.8 mg/day
Atypical antipsychotics vs. conventionals					
Guo, 2006 United States	Multi-site managed care claims database	Retrospective	January 1, 1998 to December 31, 2002	NR	Atypical Antipsychotics: Olanzapine Risperidone Quetiapine Ziprasidone Clozapine Conventional antipsychotics: Haloperidol Chlorpromazine Fluphenazine Loxapine Molindone Perphenazine Thioridazine Trifluoperazine Thiothixene Pimozide

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Gianfrancesco, 2007 United States	Bipolar and manic disorders	Mean age=36 years 50% male Ethnicity NR	NR/NR/10,037	NA/NA/10,037
Zhu, 2007 United States	Bipolar disorder	Mean age 37 years 32% male Ethnicity NR	NR NR 1516	NA NA 1516
Atypical antipsychotics vs. conventionals				
Guo, 2006 United States	An affective disorder or cyclothymia: controls and diabetics	Age: 4.47% were ≤12 years 9.74% 13-17 years 29.13% 18-34 36.65% 35-49 17.64% 50-64 2.36% ≥65 39.34% males	NR/NR/920 cases and 5258 controls	NR/NR/920 cases and 5258 controls

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Effectiveness outcomes
Gianfrancesco, 2007 United States	Hazard Ratio (95% CI) for hospitalization: Olanzapine vs risperidone: 1.00 (0.88, 1.15) Risperidone vs quetiapine: 1.19 (1.01, 1.40) Risperidone vs ziprasidone: 1.44 (0.99, 2.12) Olanzapine vs quetiapine: 1.19 (1.01, 1.40) Olanzapine vs ziprasidone: 1.45 (0.99, 2.12) Quetiapine vs ziprasidone: 1.22 (0.82, 1.81) <u>Subgroup analyses:</u> Age: 0.986 (0.982, 0.990) Gender (male vs female): 0.931 (0.827, 1.048) Substance dependence/abuse (yes vs no): 2.596 (2.307, 2.922)
Zhu, 2007 United States	Initiation of monotherapy olanzapine 51% vs. quetiapine- (36%, p < 0.01), ziprasidone- (25%, p < 0.01), and risperidone-initiated patients (40%, p < 0.01) For one year olanzapine initiated patients used this index antipsychotic as monotherapy for significantly more days (73.4) than patients initiating quetiapine (56.2, p < 0.01), risperidone (52.9, p < 0.01) or ziprasidone (36.6, p < 0.01) Annual healthcare costs $15 208 for olanzapine, $14 216 for risperidone, $18 087 for quetiapine (vs. olanzapine p < 0.01) to $18 729 for ziprasidone (vs. olanzapine p < 0.01)
Atypical antipsychotics vs. conventionals	
Guo, 2006 United States	Of the 920 cases, 41% received atypical antipsychotics: 20% olanzapine; 14% risperidone; 9% quetiapine; and 1% ziprasidone. Risk of developing diabetes was greatest among clozapine users, ziprasidone users, olanzapine users, risperidone users, patients receiving switched atypical antipsychotics, and patients receiving conventional antipsychotics. Compared to conventional antipsychotics, risk of developing diabetes was greatest among those taking clozapine, olanzapine, risperidone and quetiapine.

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Safety Outcomes	Comments
Gianfrancesco, 2007 United States	NR	
Zhu, 2007 United States	NR	
Atypical antipsychotics vs. conventionals		
Guo, 2006 United States	NR	

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow up	Interventions Mean dose
Noncomparative studies					
Clozapine					
Zarate, 1995 United States	McLean Hospital records	Retrospective recruitment prospective follow up	Unclear	At least 3 months	Clozapine at discharged: 182 mg/day follow-up: 304.4 mg/day
Olanzapine					
Chengappa, 2005 Hennen, 2004 United States	Patients in an Eli Lilly RCT doing a 1-year follow-up with Olanzapine (follow-up to Tohen 1999)	Prospective	1 year	52 weeks total: 3 weeks DB, 49 weeks open label (OL) mean: 27.9 weeks Mean duration of participation: 30.0 (+/- 19.8) weeks	Quetiapine or ziprasidone

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Noncomparative studies				
Clozapine				
Zarate, 1995 United States	Refractory bipolar disorder	Mean age: 38.6 years 53% male Ethnicity NR	193 17 17	0 0 17
Olanzapine				
Chengappa, 2005 Hennen, 2004 United States	Bipolar I mania episode or mixed state	Mean age: 39.4 years 51.7% male Ethnicity NR (values from Hennen a little different in Chengappa)	NR NR 139	NR NR 113

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Effectiveness outcomes
Noncomparative studies	
Clozapine	
Zarate, 1995 United States	CGI responders, very much or much improved: at discharged: 11(64%) follow-up: 15(88%) CGI mean score: at discharged: 2.3(0.2) follow-up: 1.8(2.2) at discharged vs follow-up, p=0.02
Olanzapine	
Chengappa, 2005 Hennen, 2004 United States	Symptomatic remission of mania during 1 year: 79 (69.9%) remission by week 8: 50% CGI-BP: remitted vs not remitted = 4.38 (0.76) vs 4.85 (0.85), p=0.006 plausible, nearly ninefold, greater rate of trial completion: remitted vs not remitted = 53% vs 6%, p<0.001 Of the 79 subjects who achieved symptomatic remission: became symptomatic again: 82.3% (65/79) failed to sustain remission for at least 2 months: 49.4% (39/79) Achieved sustained recovery: 35.4% (40/113) Time-in-remission: 19.3(15.3) weeks, 52.2 (26.5)% patients Time-in-sustained-recovery: 31.65 (13.7) weeks

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Safety Outcomes	Comments
Noncomparative studies		
Clozapine		
Zarate, 1995 United States	Side effects: 30% sedation 23% vertigo or dizziness 24% weight gain 18% salivation 6% constipation 6% tachycardia Rehospitalization rate: before starting clozapine: 0.8(1.2) follow-up during clozapine: 0.4(1.2) before vs follow-up, p=0.025	
Olanzapine		
Chengappa, 2005 Hennen, 2004 United States	Only 15% (3 women and 3 men = 6/40) who recovered did so without weight gain Body weight increase (SD) at the endpoint: +6.53 (8.9) kg Increase of BMI: 2.17 (3.0) kg/m2 to 31.0 (6.1) kg/m2 50.4% of subjects had BMI ≥30 kg/m2 (i.e., reached obesity criteria) at endpoint 33.9% of subjects experienced increases of BMI of ≥10%	30.1% of OL patients were obese to begin with (BMI ≥30 kg/m2)

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow up	Interventions Mean dose
Dennehy, 2003 United States	NR	Prospective	1998-1999	8 weeks	Olanzapine 5-12 mg
Gonzalez-Pinto, 2001 Spain	Santiago Hospital Psychiatric Unit	Prospective	March 1999 - February 1998	NR	Olanzapine 5-20 mg other antipsychotics (haloperidol and levomepromazine)

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Dennehy, 2003 United States	Bipolar I disorder	Mean age: 39 years 26.7% male Ethnicity NR	NR NR 15	5 3 15
Gonzalez-Pinto, 2001 Spain	Mania	Mean age: 37.1 years 53.4% male Ethnicity NR	86 44 44	0 0 44

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Effectiveness outcomes
Dennehy, 2003 United States	YMRS scores decreased: 14(93%) YMRS mean scores: 9.86, 2-30 point deduction IDS-C depressive symptoms: average 4.47 points reduction HAM-D: average 4 points reduction IDS-C depressive symptoms: 8 patients experienced a reduction of 1-37 points 7 patients experienced a increase of 3-16 points HAM-D: 2 patients experienced increased depression and contributed to the early withdrawal GAF: no significant change over the 8 weeks trial
Gonzalez-Pinto, 2001 Spain	olanzapine vs other antipsychotics YMRS scores improved: 29.35 vs 19.6, p=0.008 HAM-D scores improved: 15.71 vs 11.9, p=0.05 hospital length of stay: 22.14 vs 20.10 , p=0.5 Logistic regression model of variables associated with a Hamilton decrease of 80% or more: p value, odds ratio male: 0.813, 0.779 age>30: 0.009, 885.1 no. of episodes>5: 0.095, 0.127 years of illness>10: 0.114, 0.070 age at onset>25: 0.119, 0.060 suicidal attempts: 0.757, 0.717 days of hospitalization>=21: 0.791, 1.297 compulsory admission: 0.465, 0.483 olanzapine: 0.045, 11.063 lithium: 0.560, 1.785

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Safety Outcomes	Comments
Dennehy, 2003 United States	Side effects: 80% moderate to severe dry mouth 60% mild dizziness 53% edema 53% mild to moderate drowsiness 47% constipation Weight gain: Of 13 patients with more than one weight measurement: 10(77%) patients range from 0.91-7.26 kg Of 7 patients who completed at least 7 visits: average gain 2.2 kg 1 patient with a weight loss of 10.89 kg in 3 weeks, putatively due to stimulant use 6 patients who gained weights: gained average 4.39kg	
Gonzalez-Pinto, 2001 Spain	NR	

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow up	Interventions Mean dose
Janenawasin, 2002 United States	NR	Prospective	NR	9 weeks	Olanzapine 7.8 mg
McElroy, 1998 United States	NR	Prospective	NR	101.4 days	Olanzapine 14.1 mg

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Janenawasin, 2002 United States	Bipolar I, bipolar II or bipolar not otherwise specified	Mean age: 37.7 years 48% male Ethnicity NR	NR NR 25	NR NR 25
McElroy, 1998 United States	Bipolar I disorder	NR	NR NR 14	NR NR 14

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Effectiveness outcomes
Janenawasin, 2002 United States	change from baseline, mean slope CGI: -1.7, p=0.002 YMRS: -13.1, p=0.002 HDRS: -6.9, p=0.006 HARS: -4.2, p=0.0004 MADRS: -6.1, p=0.1 acute phase (W1), change from baseline, mean slope CGI: -3.9, p<0.0001 YMRS: -21.1, p=0.008 HDRS: -19.7, p=0.0002 HARS: -13.2, p=0.001 MADRS: -29.3, p<0.0001 subchronic phase (W1-9), change from baseline, mean slope CGI: -0.9, p=0.1 YMRS: -6.5, p=0.02 HDRS: 0.6, p=NS HARS: 0.4, p=NS MADRS: 5.6, p=NS 25(60%) responders with final CGI-S <= 2 Time to consistent response correlated with final olanzapine dose, p<0.02 olanzapine dosage: early vs late responders = 4.5 vs 9.4 mg/day, p=0.03
McElroy, 1998 United States	Of all 14 patients Month 1: 9(64%) much or very much improved Endpoint: 8(57%) much or very much improved Of 12 patients initiated for manic or hypomanic: Month 1: 8(67%) much or very much improved Endpoint: 7(57%) much or very much improved 3(25%) mild or no change 2(17%) much or very much worsened

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Safety Outcomes	Comments
Janenawasin, 2002 United States	17(68%) mild to moderate sedation 4(16%) moderate sedation, which affected function 14(56%) mild to moderate dry mouth 3(12%) dry mouth as problematic 11(44%) tremor 4(16%) mild sexual dysfunction 1(4%) mild akathisia baseline vs endpoint weight gain: 171(38.2) vs 178.5(38.4), p<0.0001 BMI: 24.4(4.2) vs 25.7(4.5), p=0.0003	
McElroy, 1998 United States	1(7%) bad dream 5(38%) sedation 2(14%) tremor 2(14%) dry mouth 2(14%) increased hunger/weight gain 1(7%) restlessness 1(7%) swollen hands 1(7%) nausea 1(7%) headache	

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow up	Interventions Mean dose
Vieta, 2001 Spain	Naturalistic: Clinic nr	Prospective	NR	303 days	Olanzapine 8.2 mg
Risperidone					
Bahk, 2004 Korea	81 nationwide sites in Korea	Prospective	August 2002 - December 2002	6 weeks	Risperidone 3.1 mg

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Vieta, 2001 Spain	Treatment resistant bipolar disorder	Mean age: 39.9 56.5% male Ethnicity NR	NR NR 23	6 (23%) withdrawn 1 (4.3%) lost to fu 23 analyzed
Risperidone				
Bahk, 2004 Korea	bipolar manic or hypomanic episode	Mean age: 37.9 years 45.8% male 100% Asian	NR NR 909	18 25 866

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Effectiveness outcomes
Vieta, 2001 Spain	NR
Risperidone	
Bahk, 2004 Korea	Baseline vs endpoint: YMRS: 32.9(10.8) vs 9.5(8.4), p<0.0001 CGI-S: 4.8(1.1) vs 2.1(0.8), p<0.0001 YMRS 50% or more reduction: 693(77.8%) patients

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Safety Outcomes	Comments
Vieta, 2001 Spain	Weight gain 3 (13%) Hospitalizations 3 (13%)	
Risperidone		
Bahk, 2004 Korea	22.2% headache 21.7% sedation 21.5% gastrointestinal discomfort such as nausea and constipation 11.2% fatigue 10.5% dizziness 18.6% EPS including tremor, rigidity, dystonia and involuntary muscle contraction weight gain: 1.5kg, p<0.0001 BMI increased: 0.6, p<0.0001	

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow up	Interventions Mean dose
Bowden, 2004 United States	Patients in RCT (Sachs 2002)	Prospective	NR	10 weeks	Risperidone 3.1 (+/-0.2) mg/day Risperidone adjunctive to mood stabilizers

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Bowden, 2004 United States	Bipolar manic 78.9% Bipolar mixed 21.1%	Mean age: 41.3 years 45.9% male Ethnicity: NR	NR 156 85	35 4 48

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Effectiveness outcomes
Bowden, 2004 United States	Symptomatic remission (YMRS ≤12) seen in 79% (38/48) patients at week 10 more stringent definitions of remissions: a) % with YMRS ≤8: 67% (32/48) b) % with YMRS ≤8 + HAM-D score ≤7 : 35% (17/48) Mean time to first remission: 32 days for criteria of YMRS scores <=12 Mean time to first remission: 34 days for YMRS score ≤8 + HAMD score ≤7 CGI scores: % of patients rated as "much or very much improved" increased from 59% at week 1 to 71% at week 10 HAM-D scores <=8 : 60% of patients Mean BPRS at week 1: 31.0 (n=83); mean BPRS at week 10: 29.5 (n=48)

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Safety Outcomes	Comments
Bowden, 2004 United States	Antiparkinsonian medication administered to 25.9% patients (22/85) Lorazepam administered to 7.06% patients (6/85) Mean weight gain for all groups over the 10-week OL treatment: 2.85kg All patients with any AEs: 92.9% (79/85) Extrapyramidal disorder: 29.4% (25/85) Somnolence: 29.1% (23/85) Tremor: 15.3% (13/85) Rhinitis: 15.3% (13/85) Increased saliva: 14.1% (12/85) Headache: 12.9% (11/85) Hypertonia: 12.9% (11/85) Insomnia: 11.8% (10/85) Back pain: 11.8% (10/85) Hyperkinesia: 10.6% (9/85) Fatigue: 10.6% (9/85) Dyspepsia: 9.4% (8/85) Constipation: 8.2% (7/85) Dizziness: 7.0% (6/85) Depression: 7.0% (6/85) Nausea: 7.0% (6/85) Vomiting: 4.7% (4/85) Pain: 4.7% (4.85)	

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Data Source	Prospective Retrospective Unclear	Sampling frame time period	Mean duration of follow up	Interventions Mean dose
Vieta, 2002 Spain	NR	Prospective	NR	6 weeks	Risperidone 4.9 mg

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Population	Age Gender Ethnicity	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed
Vieta, 2002 Spain	bipolar I or II disorder	Mean age: 40.7 years 40.2% male Ethnicity NR	NR NR 174	12 3 159

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Effectiveness outcomes
Vieta, 2002 Spain	Baseline vs endpoint YMRS: 26.3 vs 5.7, p<0.0001 YMRS >=50% improvement: 87% patients YMRS >=50% improvement: 76% ITT patients PANSS: total: 66.2 vs 49, p<0.0001 positive: 20.1 vs 11.7, p<0.0001 negative: 12.5 vs 10.6, p<0.0001 general: 37.1 vs 26.1, p<0.0001 HAM-D: 12.2 vs 6.6, p<0.0001 CGI: 2.6 vs 1.6, p<0.0001 CGI: improved: 22.5% patients much improved: 61.7% patients entirely symptom-free: 15.4%

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Safety Outcomes	Comments
Vieta, 2002 Spain	12(11%) experienced side effects: 3 drowsiness 3 weight gain 2 dry mouth 2 impotence 1 dizziness 1 weight loss 1 hypotension 1 impaired concentration 1 amenorrhea 6% of the adverse events were considered severe 44% were considered moderate 10(6%) initiation or exacerbation of mania 10(6%) initiation of depression	

Evidence Table 11. Quality assessment of observational studies in patients with bipolar disorder

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes prespecified and defined	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Altamura, 2008	Yes	Yes	Yes	No	Yes	Yes	NR	Yes: 4 yrs
Gianfrancesco, 2007	Yes	NA (case-control study)	Yes	NA	Yes	Unclear; limitations of using ICD-9 for diagnosis of bipolar disorder	Yes	Unclear; mean treatment episode duration NR
Guo, 2006	Yes: case-control study: controls matched on age, sex, bipolar diagnosis	NA (case-control study)	Yes; drug exposure and diabetes were pre-specified	Yes	Yes, for diabetes diagnosis and for drug consumption	Unclear; limitations of using ICD-9 for diagnosis of diabetes	yes	Unclear; exposure examined over 4 years; perhaps prior exposure could have effect
Hassan, 2007	Yes	Yes	Yes	NA	Yes	Yes	Yes	12 months
Vieta, 2001	Yes	Yes	No, definition of "weight gain" was not specified	No	No	No	NR	Yes
Zhu 2007	Yes	Yes	Yes	NA	Unclear how 'total number of days used' was calculated and how gaps in refills were handled	Unclear; limitations of using ICD-9 for diagnosis of diabetes	Yes	12 months

Evidence Table 11. Quality assessment of observational studies in patients with bipolar disorder

Author, year	Adequate sample size?	Overall adverse event assessment quality	Comments
Altamura, 2008	Yes, n=232	Poor, see comment	Study not designed to assess AEs: subjects who discontinued due to AEs were excluded from analysis.
Gianfrancesco, 2007	Yes; N=10,037	Fair	
Guo, 2006	Yes (cases 920, controls 5258)	Fair	Case control study
Hassan, 2007	Unclear - 825	Fair	
Vieta, 2001	No, 23	Fair	
Zhu 2007	Unclear - 1516	Fair	

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Aims	Literature search dates	Population included	Drugs included	Study designs included
Ballard, 2007 (Cochrane Review)	To determine whether evidence supports the use of AAPs for the treatment of aggression, agitation, and psychosis in people with Alzheimer's disease	Through December 7, 2004	Age >60; outpatients or living in care facilities; Diagnosis of Alzheimer's Disease using any commonly used criteria;	Olanzapine, quetiapine, risperidone, clozapine, amisulpride, sertindole, aripiprazole, ziprasidone	Randomized, double-blind, placebo-controlled, parallel group trials, minimum duration 6 weeks;
Kryzhanovvskaya, 2006	To review the safety of olanzapine in elderly patients with dementia	Not reported: Studies conducted from 1994-2002, including all Lilly double-blind, placebo-controlled trials conducted in this population.	Elderly patients with Alzheimer's disease, vascular dementia, mixed dementia, or dementia not otherwise specified.	Olanzapine only	Trials comparing olanzapine with placebo or conventional antipsychotics.

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Additional study eligibility criteria	Main efficacy results	Adverse events
Ballard, 2007 (Cochrane Review)	Use of a validated and published method for evaluating aggression. Excluded patients receiving other psychotropic drugs during the study	Risperidone vs placebo Total behavior: BEHAVE-AD or NPI Total (Standardized mean difference; 95% CI): 0.5 mg/day: -0.29 (-0.51, -0.06, p=0.01) 1.0 mg/day: -0.17 (-0.29, -0.05, p=0.004) 2.0 mg/day: -0.29 (-0.51, -0.07, p=0.01) BEHAVE-AD Aggressiveness (Mean difference, 95% CI): 1.0 mg/day: -0.29 (-1.28, -0.40, p=0.0002) 2.0 mg/day: -1.50 (-2.05, -0.95, p<0.0001) CMAI Total Aggressiveness (Mean difference, 95% CI): 1.0 mg/day: -1.17 (-2.02, -0.32, p=0.007) 2.0 mg/day vs 1.0 mg/day: -0.70 (-1.25, -0.15, p=0.01) BEHAVE-AD Psychosis subscore (Mean difference, 95% CI): 1.0 mg/day: -1.17 (-0.25, -0.03, p=0.01) Olanzapine 5-10 mg/day vs placebo (Mean difference, 95% CI) NPI-NH Aggression: -0.77 (-1.44, -0.10, p=0.03) NPI-NH Anxiety: -0.84 (-1.51, -0.17, p=0.01) NPI-NH Euphoria/Elation: -0.27 (-0.54, -0.00, p=0.05) Aripiprazole 2-15 mg/day vs placebo (Mean difference, 95% CI) BPRS-Psychosis: -0.66 (-1.27, -0.05, p=0.03)	Withdrawals due to adverse events vs placebo (OR; 95% CI) Risperidone 2.0 mg: 2.29 (1.27, 4.12; p=0.006) Olanzapine 5-10 mg: 3.34 (1.69, 6.59; p=0.0005) Extrapyramidal symptoms vs placebo (OR; 95% CI) Risperidone 1.0 mg: 1.78 (1.00, 3.17; p=0.05) Risperidone 2.0 mg: 3.39 (1.69, 6.80; p=0.0006) Serious cerebrovascular events vs placebo (OR; 95% CI) Risperidone 1.0 or 2.0 mg: 3.64 (1.72, 7.69; p=0.0007)
Kryzhanovvskaya, 2006	All studies were conducted by Eli Lilly	Not assessed	5 double-blind, placebo-controlled trials combined, olanzapine vs placebo Crude mortality rate: 42/1184 (3.5%) vs 7/478 (1.5%); p=0.02 Crude incidence of CVAEs: 15/1178 (1.3%) vs 2/478 (0.4%); p=0.18

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Quality Assessment
Ballard, 2007 (Cochrane Review)	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Yes 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Good
Kryzhanovvskaya, 2006	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Partially 2. Substantial effort to find relevant research? Unclear 3. Adequate assessment of validity of included studies? No 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Fair

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Aims	Literature search dates	Population included	Drugs included	Study designs included
Mazzucco, 2008	To update and systematically review the available evidence about the link between antipsychotic use in dementia and cerebrovascular adverse events	1966-206	People with dementia	Atypical and typical antipsychotics	Systematic reviews and meta-analyses of randomized controlled trials; individual RCTs not included in systematic reviews; observational studies; database analysis or ecological studies.
Schneider, 2005	To assess the evidence for increased mortality from atypical antipsychotics drug treatment for people with dementia.	1966-April 2005	Alzheimer's disease, vascular dementia, mixed dementia, or a primary dementia.	aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone	Randomized, double-blind, placebo-controlled, parallel group trials.

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Additional study eligibility criteria	Main efficacy results	Adverse events
Mazzucco, 2008	Data about the relationship between antipsychotic drug use and risk of cerebrovascular disease in people with dementia.	Not assessed	Findings of other systematic reviews: 1) 2.2% of drug-treated subjects experienced CVAEs compared with 0.8* of placebo-treated patients. Weighted relative risk statistically significant for risperidone (3.2; 95% CI 1.4 to 7.2) but not olanzapine (1.8; 95% CI 0.5 to 6.3) 2) Overall risk vs placebo was 2.13 (95% CI 1.2 to 3.75); significantly increased risk found only for risperidone (OR 3.43; 95% CI 1.6 to 7.32) 3) 1.3% of aripiprazole-treated vs 0.6% of placebo-treated patients reported CVAE. Not statistically signficant, although there was a dose response relationship in one trial of patients treated with aripiprazole. 4) No difference between olanzapoine, quetiapine, risperidone, and placebo groups in the CATIE-AD trial Non-randomized evidence: Data from large observational administrative database studies suggested no increased risk of cerebrovascular adverse events with atypical antipsychotics compared with typical antipsychotics.
Schneider, 2005	Numbers of patients randomized, dropouts, and deaths were obtainable.	Not assessed	Mortality vs placebo: Odds ratio (95% CI): aripiprazole: 1.73 (0.70, 4.30) olanzapine: 1.91 (0.79, 4.59) quetiapine: 1.67 (0.70, 4.03) risperidone: 1.30 (0.76, 2.23) Overall: 1.54 (1.06, 2.23) Withdrawal vs placebo: Risk difference, (95% CI): aripiprazole: -0.07 (-0.15, 0.01; p=0.10) olanzapine: 0.06 (-0.02, 0.15; p=0.12) quetiapine: 0.02 (-0.08, 0.11; p=0.73) risperidone: 0.03 (-0.15, 0.01; p=0.10) Overall: -0.07 (-0.03, 0.08; p=0.31)

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Quality Assessment
Mazzucco, 2008	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Yes 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Good
Schneider, 2005	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? No 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Fair

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Aims	Literature search dates	Population included	Drugs included	Study designs included
Schneider, 2006	To assess the evidence for efficacy and adverse events of atypicals for people with dementia	1966-April 2005	Alzheimer's disease, vascular dementia, mixed dementia, or a primary dementia.	aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone	Randomized, parallel-group, double-blind, placebo-controlled.
Sink, 2005	To evaluate the efficacy of pharmacological agents used in the treatment of neuropsychiatric symptoms of dementia	1966-July 2004	Patients with dementia (generally defined by DSM-IV criteria) and including Alzheimer's disease, vascular dementia, mixed, or dementia with Lewy bodies.	Any drug therapy for patients with dementia	Randomized, double-blind, placebo-controlled trials or meta-analyses of RCTs

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Additional study eligibility criteria	Main efficacy results	Adverse events
Schneider, 2006	Numbers of patients randomized and at least one outcome measure or adverse event was obtainable; unpublished studies included.	Pooled weighted mean difference vs placebo (95% CI) **Aripiprazole** BPRS Total: -2.49 (-4.05, -0.94) NPI Total: -3.63 (-6.57, -0.69) CMAI Total: -4.05 (-6.56, -1.52) **Olanzapine** BPRS Total: -0.92 (-2.48, 0.63) NPI Total: -1.74 (-4.68, 1.20) **Quetiapine** BPRS Total: -2.32 (-4.93, 0.29) PANSS-EC: -1.40 (-3.14, 0.34) CMAI: 2.20 (-6.45, 10.85) **Risperidone** BEHAVE-AD Total: -1.48 (-2.35, -0.61) CMAI: -3.00 (-4.22, -1.78) BPRS Total: 0.60 (-1.82, 3.02) NPI Total: 2.60 (-2.70, 7.90) CGI-S: -0.09 (-0.21, 0.02)	Extrapyramidal signs and symptoms: Pooled odds ratio vs placebo (95% CI) Aripiprazole: 1.29 (0.70, 2.40) Olanzapine: 1.12 (0.60, 2.07) Quetiapine: 0.92 (0.43, 1.98) Risperidone: 1.80 (1.35, 2.42)
Sink, 2005	Outcomes for neuropsychiatric symptoms (e.g., hallucinations, delusions, combativeness, verbal aggression, psychomotor agitation, wandering)	No meta-analysis Doses of 5 to 10 mg/day of olanzapine or 1.0 mg/day of risperidone appear to be at least moderately effective.	Incidence of extrapyramidal symptoms appears to be low when receiving doses of olanzapine 5 to 10 mg/day or 1.0 mg/day of risperidone, but somnolence remains a concern.

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Quality Assessment
Schneider, 2006	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Yes 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Good
Sink, 2005	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? No 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Fair

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Aims	Literature search dates	Population included	Drugs included	Study designs included
van Lersel, 2005	To systematically review the reporting of adverse events of antipsychotics used to treat BPSD in randomized, controlled trials	1980-April 2005	Diagnosis of dementia according to current international criteria for dementia (DSM-III-R, DSM-IV, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association [NINDS-AIREN]	Atypical and typical antipsychotics; others	Randomized, double-blind, placebo-controlled, or head-to-head trials

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Additional study eligibility criteria	Main efficacy results	Adverse events
van Lersel, 2005	Effect on BPSD or adverse events as a primary outcome; Intention-to-treat analysis used	Not assessed	No meta-analysis NNH for CVAEs for risperidone (from Brodaty only): 14 (95% CI 8.41) NNH for EPS was higher for atypical antipsychotics than for haloperidol in 5 of 7 studies, but not when higher doses of atypical antipsychotics were given. Increase in weight for olanzapine vs placebo in study; no increase in 2 others No increased incidence of diabetes Significantly greater cognitive deterioration in patients using quetiapine vs rivastigmine in one study.

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Quality Assessment
van Lersel, 2005	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Yes 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Good

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	494	10 weeks	Double-blind, randomized, multicenter. Nursing homes or assisted-living centers.	Age 40 or older. All patients exhibited clinically significant psychotic symptoms associated with Alzheimer's disease, vascular, or mixed dementia. Dementia diagnoses defined by NINCDS-ADRDA or DSN-IV criteria. Patients must have scored ≥ 6 (severity X frequency) on the sum of the Hallucinations and Delusions items on the NPI or NPI-NH.
Ellingrod., 2002 US (POOR)	19	8 weeks	Single-blind, nonrandomized. Four rural nursing care facilities in one city.	Age 70 or older, not receiving any psychotropic drug, with DSM-IV criteria for Alzheimer-type dementia, multiinfarct dementia, or mixed syndrome, and clinical symptoms necessitating administration of an antipsychotic drug.
Fontaine, 2003 US (POOR)	39	2 weeks	Double-blind, long-term care facilities.	Residents of extended care facilities, meeting DSM-IV criteria for dementia; medically stable and able to comply with oral, nonliquid medication; Clinical Global Impressions scale score 4 or higher and an Alzheimer's Disease Cooperative Study agitation screening scale score 25 or higher with 6 points on the delusions, hallucinations, physical aggression, or verbal aggression subscales.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Exclusion criteria	Interventions (drug, dose)	Run-in/washout Period
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	Parkinson's disease, Lewy-body dementia, Pick disease, frontotemporal dementia; or a MMSE score <5 or >24.	Risperidone, flexible dose (0.5 to 2 mg) or olanzapine, flexible dose (2.5 mg to 10 mg) or placebo	Atypical antipsychotic use was disallowed within 30 days, lithium or anticonvulsant use within 2 weeks before the placebo/washout period. Oral conventional antipsychotic use was allowed up to 3 days before randomization. 3 to 14-day placebo washout period.
Ellingrod., 2002 US (POOR)	Intracranial lesion or a history of severe head trauma.	Risperidone 0.25 mg to 3 mg or olanzapine 2.5 mg to 15 mg. Dosages determined by primary physicians.	None
Fontaine, 2003 US (POOR)	Previous neuroleptic malignant syndrome or known sensitivity to olanzapine or risperidone; current major depressive disorder or history or evidence of schizophrenia or bipolar disorder; people receiving amantadine, anorexics, carbamazepine, chloramphenicol, clonidine, erythromycin, guanabenz, guanadrel, guanethidine, guanfacine, ketanserin, methyldopa, metyrosine, narcotics, psychostimulants, reserpine, tryptophan, antiparkinsonian drugs, and benzodiazepines other than lorazepam.	Risperidone 0.5, 1.0, or 2.0 mg or olanzapine 2.5, 5.0, or 10.0 mg	3-day washout of psychotropic drugs.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	Anticholinergics (up to 6 mg per day benztropine-equivalents) and benzodiazepines (up to 4 mg per day lorazepam-equivalents) were permitted.	Mean age 78.3 65.6% female 84.0% Caucasian, 9.5% African descent, 6.5% other race/ethnicity	Baseline MMSE score 13.7 olanzapine vs 14.7 risperidone vs 15.4 placebo (p=0.021 for overall treatment group difference) 81.4% Alzheimer's dementia 5.7% vascular dementia 13.0% mixed	Number screened, eligible not reported/494 enrolled
Ellingrod., 2002 US (POOR)	Administration of other psychotropic drugs was allowed, although none of the study patients needed them.	Mean age 85 years (SD 3, range 62-99) 79% female Ethnicity not reported	Baseline MMSE score, risperidone vs olanzapine 14.09 (SD 5.48) vs 11.75 (SD 9.91)	Number screened, eligible not reported/19 enrolled
Fontaine, 2003 US (POOR)	Allowed ongoing use of anticonvulsants (except for carbazepine), anti-depressants, and cholinesterase inhibitors if they had been in stable use for 30 days prior to drug washout. Allowed episodic use of antiemetics, cough/cold preparations (except those containing diphenhydramine), inhaled, topical, or ophthalmic steroids, zolpidem, and chloral hydrate. Lorazepam allowed in doses of 0.5 to 1 mg as needed for acute agitation.	Mean age 83 (SD ~7.5) 67% female	Baseline MMSE score, risperidone vs olanzapine 9.3 SD 7.2) vs 7.2 (SD 7.0)	Number screened not reported/47 "recruited"/39 enrolled

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Outcome measures	Method of outcome assessment and timing of assessment
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	157 withdrawn/lost to followup NR/474 analyzed for primary outcome	NPI Psychosis Total, NPI Total, CGI-S Psychosis, BPRS Total, CGI-S Dementia, Cornell Total, PDS (Progressive Deterioration Scale), CMAI: Aggression.	Patients were assessed weekly for the first 2 weeks of the study and biweekly thereafter
Ellingrod., 2002 US (POOR)	0 withdrawn/0 lost to followup/19 analyzed	Brief Psychiatric Rating Scale, PANSS, Mini-Mental State Examination, Mattis Dementia Rating Scale, Abnormal Involuntary Movement Scale, Simpson-Angus Extrapyramidal Symptoms Scale, Barnes Akathisia Rating Scale, and Social Adaptive Functioning Evaluation; blood pressure	Assessment at baseline, 1 month, and 2 months by one rater.
Fontaine, 2003 US (POOR)	33 withdrawn/# lost to followup not reported/39 analyzed	Primary outcome measures: Neuropsychiatric Inventory (NPI) and Clinical Global Impressions Scale (CGI) Secondary measures: Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale, Psychogeriatric Dependency Rating Scales, Multidimensional Observational Scale for Elderly Subjects, Mini-Mental Status Examination, and Quality of Life in Late-Stage Dementia Scale	Assessment at baseline, observation on days 1,2,3,5,8,10,12, and 15 by study nurse and study physician.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Results	Method of Adverse Event Assessment
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	Mean change from baseline at endpoint, risperidone vs olanzapine: NPI Psychosis Total: ─4.2 vs ─4.0 (p=0.747) NPI Total: -0.64 vs ─9.7 vs ─11.8 (p=0.386) CGI-S Psychosis : ─0.7 vs ─0.7 (p=0.593) BPRS Total: ─3.1 vs ─3.5 (p=0.838) CGI-S Dementia: ─0.1 vs ─0.0 (p=0.246) Cornell Total: ─1.2 vs ─1.6 (p=0.596) PDS: ─2.9 vs ─2.9 (p=0.867) CMAI: Aggression: ─1.5 vs ─1.3 (p=0.781) No significant difference vs placebo for any measure	Safety assessed from spontaneous reports of treatment-emergent adverse events, using the Coding Symbols for a Thesaurus of Adverse Reaction Terms (CoSTART) dictionary, and from vital signs, ECG, analysis of laboratory tests and MMSE changes. Motor symptoms were measured with the Simpson-Angus Scale, the Barnes Akathisia Scale, and the AIMS
Ellingrod., 2002 US (POOR)	Mean change from baseline at endpoint, risperidone vs olanzapine: BPRS: -1.73 vs -0.25 (p=0.60) SAPS: -0.64 vs -0.63 (p=0.99) SANS: -1.27 vs 0.25 (p=0.27) MMSE: -2.27 vs -1.38 (p=0.53) Mattis: -10.55 vs -4.13 (p=0.29) SAFE: 2.91 vs 1.13 (p=0.35)	AIMS, Simpson-Angus Extrapyramidal Symptoms Scale, Barnes Akathisia Scale
Fontaine, 2003 US (POOR)	Mean change from baseline to day 15, risperidone vs olanzapine (p-value, visit-by-drug group interaction effect, ANOVA): CGI: -1.26 vs -1.31 (p=0.87) NPI: -23.63 vs -15.0 (p=0.31) E-BEHAVE-AD (Global Score):+0.52 vs +0.21 (p=0.45) E-BEHAVE-AD (Total Score): -1.85 vs -2.26 (p=0.81) PGDRS (Behavioral Symptoms): -4.26 vs -4.05 (p=0.91) PGDRS (Orientation): +0.47 vs -0.21 (p=0.30) PGDRS (Mobility): 0 vs -0.16 (p=0.07) MOSES: -1.74 vs -0.74 (p=0.59) QUALID: -3.53 vs -4.06 (p=0.88)	AIMS, Simpson-Angus Extrapyramidal Symptoms Scale, Barnes Akathisia Scale

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Adverse events	Total withdrawals/ Withdrawals due to AEs
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	On Simpson-Angus Scale, both groups increased more than placebo; greater increase in risperidone patients (+0.9 olanzapine vs +1.6 risperidone, p=0.02). No changes on AIMS or Barnes. CVAEs: 2.5% olanzapine, 2.0% risperidone (NS) Olanzapine vs risperidone vs placebo Mortality: 2.9% vs 2.0% vs 1.1% (NS) Falls: 11.3% vs 9.2% vs 6.4% (NS) Pneumonia: 2.0% vs 0% vs 2.1% (NS) Both active treatments associated with significantly higher incidences of somnolence, urinary incontinence, and hostility relative to placebo.	Overall: 31.1% risperidone, 37.7% olanzapine, 20.2% placebo Due to adverse events: Not reported by group. Most common AEs leading to withdrawal were agitation (N=6), psychotic symptoms, (N=6), somnolence (N=5), and accidental injury (N=5)
Ellingrod., 2002 US (POOR)	Change from baseline on AIMS at endpoint, risperidone vs olanzapine: -0.18 vs 0.375 (p=0.32) Change from baseline on Simpson-Angus at endpoint, risperidone vs olanzapine: 3.0 vs 3.25 (p=0.93)	Overall: 31.1% risperidone, 37.7% olanzapine, 20.2% placebo Due to adverse events: NR
Fontaine, 2003 US (POOR)	Change from baseline on AIMS (% rating of minimal or mild), risperidone vs olanzapine: no change on either (p=0.52) Change from baseline on Simpson-Angus, risperidone vs olanzapine: 0.12 vs 0.17 (p=0.44) Change from baseline on Barnes Akathisia Scale: (% with a rating of questionable or mild) risperidone 0.5, 1.0, or 2.0 mg: no change (6% to 6%) olanzapine 2.5, 5.0, or 10.0 mg: +5% (6% to 11%) (not analyzed, too few frequencies) olanzapine: 1 stroke No significant change in weight in either group. 113 adverse events, 31 patients had at least one adverse event. Olanzapine: 1 patient had 2 serious adverse events (asystole followed by brain stem stroke 6 days later) 12 falls: 2 result of being pushed. Of 10 spontaneous falls, 6 olanzapine, 4 risperidone (p=0.62)	Overall: 20% olanzapine, 11% risperidone. Due to adverse events: 4 olanzapine (1 rash + elevated blood pressure, pulse, white blood cell count and temperature; 2 unsteady gait or falls; 1 diaphoresis, fainting, and asystole) vs 0 risperidone.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria
Gareri, 2004 Italy (POOR)	60	8 weeks	Double-blind, setting not reported	Age 65 or older, with DSM-IV diagnoses of Alzheimer's disease, vascular dementia, or a combination of both; NPI score of at least 24.
Mulsant, 2004 US (POOR)	86	6 weeks	Double-blind, multicenter, long-term care facilities	Over age 55, with probable Alzheimer's disease, probable vascular dementia, or probable dementia of mixed etiology (by DSM-IV criteria); duration of illness of at least 1 year; MMSE scores at study entry between 7 and 26; definite psychotic symptoms, as defined by NPI frequency X severity score of >=4 on delusions, hallucinations, or both.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Exclusion criteria	Interventions (drug, dose)	Run-in/washout Period
Gareri, 2004 Italy (POOR)	NR	Risperidone 1 mg, olanzapine 5 mg, or promazine 50 mg; if no clinical response after 4 weeks, dose could be increased to 2 mg risperidone, 10 mg olanzapine, or 100 mg promazine.	10-day washout
Mulsant, 2004 US (POOR)	Presence of delirium at the time of study entry as defined by the Confusion Assessment Method, an inability to swallow oral medication, a probable or definite diagnosis of psychosis prior to the onset of dementia, and an inability to otherwise cooperate with the study procedures.	Risperidone 0.25 mg/day for the first 3 days, followed by an increase to 0.5 mg/day for days 3 through 6. Starting at day 7, dose increased to 0.75 mg/day until day 10, after which the investigator could increase the dose by 0.25 mg/day every 4 days if there was an insufficient clinical response. Total allowable dose 1.5 mg/day Olanzapine starting dose 2.5 mg/day and the same titration schedule as above, with a maximum possible dose of 10 mg/day.	3-day washout, 7-day single-blind placebo run-in.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
Gareri, 2004 Italy (POOR)	Concomitant use of other antipsychotics, antidepressants, or mood stabilizers was avoided. Lorazepam (1 to 3 mg/day) could be given as needed until the end of the first 2 weeks.	Mean age 78.9 55% female Ethnicity not reported	Not reported	NR/NR/60
Mulsant, 2004 US (POOR)	Lorazepam allowed for 4 days in any 7-day period for the treatment of agitation, at a maximum dose of 3 mg/day.	Mean age 83.8 78% female 77.6% white, 17.6% Hispanic, 5% black	Baseline MMSE score, risperidone vs olanzapine 13.7 (SD 5.05, range 7-25) vs 13.2 (SD 4.79, range 7-25) 81.2% Alzheimer's dementia 7.0% vascular dementia 11.8% mixed Length of hospitalization risperidone: 11.9 months (SD 13.5) olanzapine: 27.1 months (SD 34.6)	NR/NR/86

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Outcome measures	Method of outcome assessment and timing of assessment
Gareri, 2004 Italy (POOR)	NR/NR/60	Primary outcome measure: NPI	Assessment at baseline, 4 and 8 weeks.
Mulsant, 2004 US (POOR)	17/NR/85	Primary outcome measures: Udvalg for Kliniske Undersogelser (UKU) rating scale measuring peripheral anticholinergic effects, or a site report of a somnolence adverse event. Efficacy outcomes: NPI; abbreviated cognitive assessment.	Assessments at screening, baseline, and then at weekly periods for the duration of the trial. Cognitive assessments occurred at baseline and weeks 3 and 6 (or early termination).

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Results	Method of Adverse Event Assessment
Gareri, 2004 Italy (POOR)	Complete regression of symptoms at 8 weeks (NPI): risperidone: 14/20 (70%) (6 men, 8 women) olanzapine: 16/20 (80%) (8 men, 8 women) promazine: 13/20 (70%) (7 men, 6 women) Partial response at 8 weeks (NPI) (defined differently for different groups): risperidone: 2/20 (10%) (1 man, 1 woman) olanzapine: 4/20 (80%) (3 men, 1 woman) No response: risperidone: 1/20 (70%) (1 woman, drug interrupted at 4th week because of hypotension and confusion) promazine: 7/20 (70%) (2 men, 5 women)	Hoehn and Yahr Scale used for evaluating parkinsonism, administered at baseline, 4 weeks, and 8 weeks.
Mulsant, 2004 US (POOR)	NPI scores: Statistically significant change from baseline for both olanzapine and risperidone on overall NPI frequency X severity, hallucinations and delusions, and occupational disruption items, but no between-group differences (data not reported).	Udvalg for Kliniske Undersogelser (UKU) rating scales measuring peripheral anticholinergic effects (including visual accommodation disturbances, dry mouth, constipation, micturition disturbances, and palpitations) or a site report of a somnolence adverse event. ESRS

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Adverse events	Total withdrawals/ Withdrawals due to AEs
Gareri, 2004 Italy (POOR)	Extrapyramidal symptoms not reported. Main side effects: olanzapine: somnolence and weight gain (32%), dizziness and constipation (16%), postural hypotension (8%), akathisia (4%), and worsening of glycemic levels in one diabetic patient (4%) risperidone: hypotension and somnolence (20%), dyspepsia (12%), sinus tachycardia, asthenia, constipation, EPS (8%) increase of libido and disinhibition, abdominal pain and insomnia (4%).	Not reported
Mulsant, 2004 US (POOR)	For total ESRS scores, no statistically significant changes with either risperidone or olanzapine and NSD between the 2 treatments. Results for individual subscales were equivalent to the overall analyses (data not reported). No between-group differences in UKU scale or in somnolence adverse events.	Overall: 19.8% Due to adverse events: 4 risperidone vs 2 olanzapine (p=0.428)

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria
Rainier, 2007 Austria (FAIR)	72	8 weeks	Multicenter Outpatients	Age 55-85 years (female patients had to be at least 2 years postmenopausal); diagnosis of dementia of Alzheimer's, vascular, mixed, or fronto-temporal lobe type; behavioral disturbances, NPI Part 1 score in sub-items relating to delusions, hallucinations, agitation/aggression, disinhibition and aberrant motor behavior, and an MMSE total score of 10-26, be able to ingest oral medication and willing to complete all aspects of the study, either alone or with the aid of a responsible caregiver. Required to live with someone for the duration of the study or had substantial daily contact with a caregiver.
Schneider, 2001 Schneider, 2006 Ismail, 2007 Zheng, 2009 Sultzer, 2008 US CATIE Trial (Phase 1) (FAIR)	421	Up to 36 weeks	Double-blind, multicenter, placebo-controlled Outpatients or assisted living facilities	Dementia of the Alzheimer's type or probable Alzheimer's disease ; MMSE score between 5 and 26 ; ambulatory, living at home or in an assisted-living facility. Delusions, hallucinations, aggression, or agitation that developed after the onset of dementia and was severe enough to disrupt their functioning and justify treatment with antipsychotic drugs. Signs and symptoms of psychosis, aggression, or agitation had to have occurred nearly daily during the previous week or at least intermittently for 4 weeks. During the week before they were randomized, a severity rating of at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior on the BPRS. Alternatively, a frequency rating of "often" or "more frequently" and a severity rating oat least "moderate" for delusions, hallucinations, agitation, or "aberrant motor behavior" in the NPI. A study partner or caregiver who had regular contact with the patient was required to participate in the assessments.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Exclusion criteria	Interventions (drug, dose)	Run-in/washout Period
Rainier, 2007 Austria (FAIR)	Participation in any other drug trial within 4 weeks of the first study visit; known or suspected hypersensitivity to quetiapine or risperidone; evidence of chronic and/or severe disease; contraindications as detailed in the country-specific Prescribing Information; history of nonadherence, use of other antipsychotics; medical history of advanced, severe or unstable disease of any type that could interfere with study, current diagnosis of uncontrolled seizure disorder, active peptic ulceration, severe or unstable cardiovascular disease, acute or severe asthmatic conditions, clinically significant abnormalities on any of the following evaluations: cardiovascular, vital signs for their age, physical examination, ECG, having an authorized representative appointed by the responsible public authority; National Institute for Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association exclusion criteria (sudden apoplectic onset of dementia, focal neurological findings, and seizures or gait disturbances at the onset of or very early in the course of illness).	Quetiapine (50 mg to 400 mg/day); mean dose 77 mg (SD 40 mg) Risperidone (0.5 mg to 4 mg/day); mean dose 0.9 mg (SD 0.3 mg)	Not reported
Schneider, 2001 Schneider, 2006 Ismail, 2007 Zheng, 2009 Sultzer, 2008 US CATIE Trial (Phase 1) (FAIR)	Diagnosis of a primary psychotic disorder, delirium, other dementia such as vascular dementia or Lewy-body dementia, or psychosis, agitation, or aggression that could be better accounted for by another medical condition, medication, or substance abuse. If they required psychiatric admission, were suicidal, were going to receive treatment with a cholinesterase inhibitor or antidepressant medication, had previously been treated with two of the three atypical antipsychotic drugs under study, or had contraindications to any of the study drugs.	Doses were adjusted as clinically indicated by study physicians. Mean daily dose (range) at last dose: olanzapine: 5.5 mg (0-17.5) quetiapine: 56.5 mg (0-200) risperidone: 1.0 mg (0-2) placebo	Not reported

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled
Rainier, 2007 Austria (FAIR)	Allowed antipsychotics prothipendyl 80 mg/day and dixyrazin 25 mg/day, or tranquilizers zolpidem 10 mg/day triazolam 0.25 mg/day, and oxazepam 15-50 mg/day	Mean age 78 years 58.5% female Race not reported	66.2% Alzheimer's dementia, 13.8% mixed type, 10.8% vascular dementia, 9.2% other dementia (multi-infarct, fronto-temporal lobe dementia syndrome, Lewy body dementia)	NR/NR/72
Schneider, 2001 Schneider, 2006 Ismail, 2007 Zheng, 2009 Sultzer, 2008 US CATIE Trial (Phase 1) (FAIR)	To treat difficult behaviors during the trial, study physicians could prescribe a benzodiazepine or oral or parenteral haloperidol.	Mean age 77.9 (7.5) 56% female 79% white, 18% black, 3% other race	73% lived in own home, 16% in family's home, 10% assisted living facility, 2% other residence	521/471/421

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Number withdrawn/ lost to fu/analyzed	Outcome measures	Method of outcome assessment and timing of assessment
Rainier, 2007 Austria (FAIR)	6/1/65	Primary outcome: change from baseline in NPI Part 1 (neuropsychiatric disturbances) and Part 2 (caregiver burden and distress). CMAI CGI-I CGI-Efficacy index MMSE Age-adjusted Concentration Test	Baseline, week 4, week 8
Schneider, 2001 Schneider, 2006 Ismail, 2007 Zheng, 2009 Sultzer, 2008 US CATIE Trial (Phase 1) (FAIR)	344/0/416	Time to discontinuation for any reason (primary outcome) CGI-C at week 12 Time to discontinuation for lack of efficacy Time to discontinuation for adverse events, intolerability, or death Change in metabolic parameters	Not described

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Results	Method of Adverse Event Assessment
Rainier, 2007 Austria (FAIR)	Quetiapine vs risperidone No difference between groups on any of the NPI scores NPI score at week 8 (between-group p-value not reported) NPI Part 1: 17.5 vs 16.6 (both p<0.001 vs baseline) NPI Part 2: 27.7 vs 26.7 (both p<0.05 vs baseline) NPI Parts 1+ 2 sum of scores: 46.7 vs 44.1 (both p<0.001 vs baseline) CMAI scores at week 8: 55.67 vs 48.97; p=0.412 CGI-I: 35.3% vs 38.8% rated 'improved' or 'very much improved' (NS) CGI-Efficacy index response to treatment: 70.6% vs 71.0%	Incidence of AEs elicited by request, spontaneous report or observation from the patient, caregiver, or investigator. Simpson-Angus scale, ECG, physical examination (including body weight) and vital signs
Schneider, 2001 Schneider, 2006 Ismail, 2007 Zheng, 2009 Sultzer, 2008 US CATIE Trial (Phase 1) (FAIR)	Discontinuation for any reason: olanzapine: 79/99 (80%) quetiapine: 77/94 (82%) risperidone: 65/84 (77%) placebo: 118/139 (85%) p=0.52 Discontinuation for lack of efficacy: olanzapine: 39% quetiapine: 53% risperidone: 44% placebo: 70% olanzapine vs risperidone: Hazard ratio 0.84 (95% CI 0.53, 1.32) olanzapine vs quetiapine: Hazard ratio 0.63; (95% CI 0.41, 0.96; p=0.02) Response based on CGI-C score at week 12 (p vs placebo): olanzapine: 32% quetiapine: 26% risperidone: 29% placebo: 21% p=0.22 Worsening of symptoms in Olanzapine group compared to Quetiapine in BPRS withdrawn depression factor LSM differences=0.3, 95% CI=0.1 to 0.5, p=0.009	Assessed by eliciting information about the occurrence of AEs. Weight, prolactin, glucose, cholesterol, and triglyceride levels were measured at weeks 12, 24, and 36.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Adverse events	Total withdrawals/ Withdrawals due to AEs
Rainier, 2007 Austria (FAIR)	Quetiapine vs risperidone: Any AE: 57.9% vs 44.1% Serious AEs: 7.9% vs 2.9% No deaths or CVAEs Mean change from baseline in Simpson-Angus scale score: + 0.06 quetiapine vs +0.35 risperidone (both NS) No significant change in body weight	10.5% quetiapine, 8.8% risperidone/ 5.3% quetiapine, 2.9% risperidone
Schneider, 2001 Schneider, 2006 Ismail, 2007 Zheng, 2009 Sultzer, 2008 US CATIE Trial (Phase 1) (FAIR)	Olanzapine vs quetiapine vs risperidone vs placebo: Any serious AE: 14% vs 18% vs 11% vs 13% p=0.35 Cerebrovascular accident or TIA: 2% vs 1% vs 1% vs 1% p=0.92 Death: 1% vs 3% vs 1% vs 2% p=0.68 Any severe AE: 17% vs 26% vs 14% vs 15% p=0.11 Parkinsonism or EPS: 12% vs 2% vs 12% vs 1% p<0.001 Rate of change (SE) in metabolic measures per week of treatment Weight (pounds) Olanzapine: 0.12 (0.06) p=0.032, Quetiapine: 0.14 (0.06), p=0.019, Risperidone: 0.10 (0.06), p=0.07 HDL Cholesterol (mg/dl) olanzapine: -0.19 (0.07), p=0.0004, Quetiapine: -0.09(0.07), p=0.19, Risperidone=0.03 (0.07), p=0.68 Triglyceride (mg/dl) Olanzapine: 0.42 (0.59), p=0.48, Quetiapine: 0.55 (0.63), p=0.38, Risperidone: 0.43 (0.65), p=0.51 Glucose Olanzapine: 0.10 (0.11), p=0.37, Quetipaine:0.12(0.12), p=0.32, Risperidone: 0.24(0.13), 0.06 Magnitude of weight gain (pounds) after 12 weeks Olanzapine: 1.4 ,Quetiapine: 1.7, Risperidone: 1.2	82% withdrew Discontinuation because of intolerance, adverse events, or death: Hazard ratio vs placebo (95% CI): olanzapine: 24%: 4.32 (1.84, 10.12) quetiapine: 16%: 3.58 (1.44, 8.91) risperidone: 18%: 3.62 (1.45, 9.04) placebo: 5%

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Yes	Yes	Yes; 10 point difference in favor of placebo for severe impairment battery (Sign NR)	Yes	Yes	Yes	Yes
Brodaty, 2003 Frank, 2004 Australia, New Zealand	Yes	Not reported	Yes, but baseline data reported only on included sites (excludes patients at 1 site with 32 patients excluded due to non-adherence with documentation procedures)	Yes	Yes	Not reported	Yes
Chan, 2001 Hong Kong	Method not described	Not reported	More women in haloperidol group (83% vs 62%), otherwise similar	Yes	Yes	Not reported	Yes
De Deyn, 1999 Multiple European countries	Yes	Not reported	Yes	Yes	Yes	Not reported	Yes
De Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa	Method not reported	Not reported	Yes	Yes	Yes	Not reported	Yes

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Attrition, yes Crossover, no Adherence, no Contamination, no	Potentially, greater loss to follow-up in tx groups, Sign NR Lost to Follow-up: RIS: 10 QUE: 8 Placebo: 1	Yes	No	Fair
Brodaty, 2003 Frank, 2004 Australia, New Zealand	Attrition yes, others reported combined for each group.	Yes (27% risperidone vs 33% placebo)	No	Yes- all patients from one site (N=32) excluded due to non-adherence with documentation.	Fair
Chan, 2001 Hong Kong	Attrition yes/others NR	No	No- 3/58 not analyzed (5%).	No	Fair
De Deyn, 1999 Multiple European countries	Attrition and contamination yes/crossovers and adherence no.	Yes: 121/344 (35%) discontinued: 41% risperidone, 30% haloperidol, 35% placebo	Yes	No	Fair
De Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa	Attrition and adherence yes/crossovers and contamination no.	No	No (results on 642 of 652 randomized)	Yes- 652 randomized, patient disposition reported for 649.	Fair

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Funding	Comments
Ballard, 2005 UK Quetiapine and rivastigmine Fair	General donations to Clive Ballard [first author] research programme and profits from previously completed commercially funded clinical trials with additional support from the Alzheimer's Research Trust.	
Brodaty, 2003 Frank, 2004 Australia, New Zealand	Supported by Janssen-Cilag Australia and Johnson & Johnson; first author a consultant for Janssen and AstraZeneca; has received grant/research support and honoraria from Janssen, and serves on the speakers/advisory board for Janssen. Other authors have received support from Janssen, Lilly, Bristol-Myers. 2 authors employees of Johnson & Johnson.	
Chan, 2001 Hong Kong	Sponsored by Janssen Research Foundation	
De Deyn, 1999 Multiple European countries	Supported in part by a grant from the Janssen Research Foundation.	
De Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa	Sponsored by Eli Lilly and Company; corresponding author employed by Lilly Research Laboratories.	

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Yes	Yes	Yes; 10 point difference in favor of placebo for severe impairment battery (Sign NR)	Yes	Yes	Yes	Yes
Deberdt 2005 Multicenter, 64 centers Olanzapine vs. Risperidone and placebo	Method not reported	Not reported	Differences in age, time of diagnosis, onset of symptoms; 17% in the olanzapine arm had mixed dementia compared with 10% in the risperidone or placebo arms	Yes	Reported as double-blind, but not specified	Reported as double-blind, but not specified	Yes
Deberdt, 2005 US	Method not described	Not reported	MMSE score (olanzapine 13.7, risperidone 14.7, placebo 15.4) significantly lower for olanzapine vs placebo, but NSD for risperidone vs olanzapine	Yes	Not reported (described as double blind)	Not reported (described as double blind)	Not reported (described as double blind)
Ellingrod, 2002 US	Not randomized	No	Olanzapine group lower MMSE (11.75 vs 14.09)	Yes	Yes	No	Yes
Fontaine, 2003 US	Not clear if randomized	Not reported	More risperidone patients using antidepressants prior to study (58% vs 25%)	Yes	Yes	Not reported	Yes

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Attrition, yes Crossover, no Adherence, no Contamination, no	Potentially, greater loss to follow-up in tx groups, Sign NR Lost to Follow-up: RIS: 10 QUE: 8 Placebo: 1	Yes	No	Fair
Deberdt 2005 Multicenter, 64 centers Olanzapine vs. Risperidone and placebo	Attrition, yes Crossovers, no Adherence, no Contamination, no	Unable to determine 62.8% completed olanzapine arm of phase II ?% completed risperidone arm of phase II 79.8% completed placebo arm of phase II ~16% in olanzapine arm discont'd due to AE ~9% in risperidone arm ~3% in placebo arm	Not ITT for entire population but ITT and LOCF was used for NPI, CGI in Alzheimer's Dementia patients only	Not reported	Poor (see comments)
Deberdt, 2005 US	Attrition yes, others no	No	No- analyzed patients with a baseline and at least one post-baseline score for the primary outcome, using a LOCF analysis (474 of 494 randomized; 96.0%)	NR	Fair
Ellingrod, 2002 US	NR	NR	Yes	NR	Poor
Fontaine, 2003 US	Attrition yes/others NR	20% olanzapine vs 11% risperidone discontinued	Not clear	No	Poor

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Funding	Comments
Ballard, 2005 UK Quetiapine and rivastigmine Fair	General donations to Clive Ballard [first author] research programme and profits from previously completed commercially funded clinical trials with additional support from the Alzheimer's Research Trust.	
Deberdt 2005 Multicenter, 64 centers Olanzapine vs. Risperidone and placebo	Eli Lilly	Unclear how many patients completed the risperidone arm; though authors report a washout period they did not report if these patients were naïve to the study meds administered in this study; considerable 'selective reporting' of results
Deberdt, 2005 US	Eli Lilly	
Ellingrod, 2002 US	Supported by the 1999 American College of Clinical Pharmacy Research Award.	
Fontaine, 2003 US	Supported by Eli Lilly and Company.	

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Yes	Yes	Yes; 10 point difference in favor of placebo for severe impairment battery (Sign NR)	Yes	Yes	Yes	Yes
Gareri, 2004 Italy	Method not described	Not reported	Baseline characteristics not reported (except age and sex)	Yes	Yes	Not reported (described as double blind)	Not reported (described as double blind)
Katz, 1999 US	Yes	Not reported	MMSE mean scores higher in risperidone 2 mg group than placebo; other differences not significant.	Yes	Yes	Not reported	Yes
Kennedy, 2005 US Olanzapine Fair	Unclear; states 2:1 ratio	Unclear	Yes	Yes	NR	NR	NR
Meehan, 2002 Multinational, 38 centers in 3 countries Olanzapine IM vs. Lorazepam IM vs. Placebo IM	Method not reported	Not reported	Did not report baseline % of patients with Alzheimer's and Vascular disease; numerical differences by ~9% in gender between olanzapine 2.5 and 5mg arms; >1 point difference in baseline CMS, PANSS-EC, MMSE scores between olanzapine, placebo, and lorazepam	Yes	Reported as double-blind, but not specified	Reported as double-blind, but not specified	Reported as double-blind, but not specified

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Attrition, yes Crossover, no Adherence, no Contamination, no	Potentially, greater loss to follow-up in tx groups, Sign NR Lost to Follow-up: RIS: 10 QUE: 8 Placebo: 1	Yes	No	Fair
Gareri, 2004 Italy	NR	NR	Yes	No	Poor
Katz, 1999 US	Attrition yes, others no.	No	No: results on 617/625 at endpoint, 435/625 at week 12.	No	Fair
Kennedy, 2005 US Olanzapine Fair	Attrition, yes Crossover, no Adherence, no Contamination, no	Differential, borderline high More patients completed in placebo (73%) vs. olanzapine (60%); non-completers 27% in placebo vs. 40% in olanzapine	Yes; LOCF	No	Fair
Meehan, 2002 Multinational, 38 centers in 3 countries Olanzapine IM vs. Lorazepam IM vs. Placebo IM	Attrition, yes Crossovers, yes 31 in placebo-arm received olanzapine 5mg. Adherence, no Contamination, no	No, 91.7% completed the study (~8% discontinued and ~11% were cross-over patients who were excluded)	Yes for primary and most secondary endpoints; LOCF used for PANSS-EC; did not specify what methods were used for missing data for the other efficacy points	Yes 31 placebo-crossover patients who received a 3rd injection with olanzapine 5mg	Poor (see comments)

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Funding	Comments
Ballard, 2005 UK Quetiapine and rivastigmine Fair	General donations to Clive Ballard [first author] research programme and profits from previously completed commercially funded clinical trials with additional support from the Alzheimer's Research Trust.	
Gareri, 2004 Italy	Ministry of Health	
Katz, 1999 US	Supported by a grant from the Janssen Research Foundation.	
Kennedy, 2005 US Olanzapine Fair	Eli Lilly	
Meehan, 2002 Multinational, 38 centers in 3 countries Olanzapine IM vs. Lorazepam IM vs. Placebo IM	Eli Lilly	unclear regarding baseline disease distribution (how many had AD and VD?); did not report results for 2ndary endpts comparing olanzapine to lorazepam as they were prespecified (see abstract); did not specify exclusion criteria or indicate if these patients were naive to study meds given

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Yes	Yes	Yes; 10 point difference in favor of placebo for severe impairment battery (Sign NR)	Yes	Yes	Yes	Yes
Meehan, 2002 US, Russia, and Romania	NR	NR	Yes (but no details)	Yes	NR (described as double blind)	NR (described as double blind)	NR (described as double blind)
Mintzer, 2006 US	Yes	Yes	No differences, but baseline characteristics reported only for analyzed population only (416/473 randomized)	Yes	Reported as double-blind, but not specified	Reported as double-blind, but not specified	Reported as double-blind, but not specified
Moretti, 2005 Italy	N/A; controlled trial in which patients were manually divided into two groups	N/A	Yes	Yes	Unclear, open study and no information about rater blinding	No, open study	No, open study
Mulsant, 2004 US	Method not described	Not reported	Differences in sex (71% risperidone vs 84% olanzapine female), diagnosis (76% vs 86% Alzheimer's disease), and length of institutionalization (11.9 vs 27.1 months)	Yes	Not reported (described as double blind)	Not reported (described as double blind)	Not reported (described as double blind)
Paleacu 2008	NR	NR	NR	Yes	NR (described as double blind)	NR (described as double blind)	NR (described as double blind)

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Attrition, yes Crossover, no Adherence, no Contamination, no	Potentially, greater loss to follow-up in tx groups, Sign NR Lost to Follow-up: RIS: 10 QUE: 8 Placebo: 1	Yes	No	Fair
Meehan, 2002 US, Russia, and Romania	Attrition yes, others no.	No	Yes	No	Fair
Mintzer, 2006 US	Attrition and adherence yes, others no.	No (<1%)	No: efficacy analyses on 416/473 randomized patients (87.9%)	Yes, 57 patients excluded for non-compliance at site (7) or not psychotic at baseline (50)	Fair
Moretti, 2005 Italy	Yes, No, No, No	None	Excluded 4 (1%) due to refusal to participate and 6 (2%) due to not having a caregiver that could guarantee compliance	NR	Fair
Mulsant, 2004 US	Attrition yes (but not reported by group), others no.	Unable to determine	No (excluded 1 olanzapine patient with no postbaseline data)	No	Poor
Paleacu 2008	Yes, No, No, No	No/No 68% completed trial	No	No	Fair

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Funding	Comments
Ballard, 2005 UK Quetiapine and rivastigmine Fair	General donations to Clive Ballard [first author] research programme and profits from previously completed commercially funded clinical trials with additional support from the Alzheimer's Research Trust.	
Meehan, 2002 US, Russia, and Romania	Eli Lilly	
Mintzer, 2006 US	Johnson & Johnson	
Moretti, 2005 Italy	NR	
Mulsant, 2004 US	Janssen	
Paleacu 2008	AstraZeneca	

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Yes	Yes	Yes; 10 point difference in favor of placebo for severe impairment battery (Sign NR)	Yes	Yes	Yes	Yes
Pollock 2007	Unclear, randomization schedule determined by unblinded statistician	NR	No, gender differences and differences on NBRS total scores	Yes	Yes	Yes	Yes
Rainer, 2007 Austria quetiapine versus risperidone Fair	Unclear; states computer generated scheme	Only assessors blinded	Yes	Yes	Yes	No	No
Rappaport 2009	Unclear	Unclear	Yes, except for one of the four groups had all white participants	Yes	NR (described as double blind)	NR (described as double blind)	NR (described as double blind)
Savaskan, 2006 open-label comparative study haloperidol vs. quetiapine Fair-Poor	Unclear	Unclear	Yes; only sex and age provided	Yes	unclear	unclear	No
Schneider, 2006 US, 45 sites [CATIE-AD] olanzapine, quetiapine, risperidone, placebo Phase I stated as double-blind Fair	Yes permuted blocks of nine per site without stratification; interactive voice-response telephone system.	Yes	Yes	Yes	Unclear	Unclear	Yes

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Attrition, yes Crossover, no Adherence, no Contamination, no	Potentially, greater loss to follow-up in tx groups, Sign NR Lost to Follow-up: RIS: 10 QUE: 8 Placebo: 1	Yes	No	Fair
Pollock 2007	Yes, No, No, No	No/Yes 43% completed trial	No	6 people excluded for "administrative" reasons	Fair
Rainer, 2007 Austria quetiapine versus risperidone Fair	Attrition, yes Crossover, no Adherence, yes Contamination, no	No/No 10% overall	Yes; LOCF	Yes; analysis accounted for these	Fair
Rappaport 2009	Yes, No, No, No	No/No 98% completed trial	Yes, LOCF	No	Fair
Savaskan, 2006 open-label comparative study haloperidol vs. quetiapine Fair-Poor	Attrition, yes Crossover, no Adherence, yes Contamination, no	Differential, No High, Yes	No	No	Fair-Poor
Schneider, 2006 US, 45 sites [CATIE-AD] olanzapine, quetiapine, risperidone, placebo Phase I stated as double-blind Fair	Attrition, yes Crossover, yes Adherence, yes Contamination, no	Differential, No High, Yes Discontinuation rates 77 - 85%	Yes	No	Fair

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Funding	Comments
Ballard, 2005 UK Quetiapine and rivastigmine Fair	General donations to Clive Ballard [first author] research programme and profits from previously completed commercially funded clinical trials with additional support from the Alzheimer's Research Trust.	
Pollock 2007	US Public Health Service	
Rainer, 2007 Austria quetiapine versus risperidone Fair	AstraZeneca	Small sample; majority of patients received concomitant medication; patients and investigators were aware of randomization outcome
Rappaport 2009	Bristol-Myers Squibb & Otsuka Pharmaceutical Co,, Ltd.	
Savaskan, 2006 open-label comparative study haloperidol vs. quetiapine Fair-Poor	AstraZeneca (Switzerland) & Swiss National Science Foundation Research Professorship	Short study, small sample size
Schneider, 2006 US, 45 sites [CATIE-AD] olanzapine, quetiapine, risperidone, placebo Phase I stated as double-blind Fair	NIMH; Eli Lilly, AstraZeneca, Forest Pharmaceuticals and Janssen Pharmaceutica supplied drugs, were not involved in design, analysis, or interpretation.	Patients were allowed to discontinue study drug in Phase I, to be assigned to a different group in Phase II; this may have created greater discontinuation rates. Difficult to interpret. Randomized Phase I/ Discontinued / Enrolled in Phase II Olanzapine group: 100/ 80 / 57 Quetiapine group: 94/ 77/ 54 Risperidone group: 85/ 66/ 49 Placebo group: 142/ 121/ 93 Placebo group more likely to not discontinue compare to 3 anti-psychotic tx groups (sign)

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Yes	Yes	Yes; 10 point difference in favor of placebo for severe impairment battery (Sign NR)	Yes	Yes	Yes	Yes
Street et al., 2000 US	Yes	Not reported	Yes	Yes	Yes	Not reported	Yes
Streim 2008	NR	NR	Yes	Yes	NR (described as double blind)	NR (described as double blind)	NR (described as double blind)
Suh, 2004 South Korea	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Tariot, 2004 (poster) US	Method not reported	Not reported	Differences in mean age between groups: quetiapine 81.92; haloperidol 83.55; placebo 83.93 (p=0.042 quetiapine vs. haloperidol)	Yes	Yes	Not reported	Yes
Tariot, 2006 US, 47 sites stated as double-blind quetiapine vs. haloperidol vs. placebo Fair	Unclear; 3:1 ratio	Unclear	Yes	Yes	Unclear	Unclear	Yes

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Attrition, yes Crossover, no Adherence, no Contamination, no	Potentially, greater loss to follow-up in tx groups, Sign NR Lost to Follow-up: RIS: 10 QUE: 8 Placebo: 1	Yes	No	Fair
Street et al., 2000 US	Attrition yes, others no.	No	Yes (6/206 not analyzed, able to calculate)	1 (placebo) did not receive intervention.	Good
Streim 2008	Yes, No, No, No	66% completed in aripiprazole group 51% complete in placebo group	Yes, LOCF	No	Fair
Suh, 2004 South Korea	Attrition yes/others NR	No	No; 6/120 (5%) excluded from analysis.	No	Fair
Tariot, 2004 (poster) US	NR	High	Unclear	NR	Poor
Tariot, 2006 US, 47 sites stated as double-blind quetiapine vs. haloperidol vs. placebo Fair	Attrition, yes Crossover, no Adherence, no Contamination, no	Differential, No High, Yes Discontinued: Que 32%; Hal 41%; Placebo 36%	Yes, LOCF	Yes; "investigator discretion"; Que 4, Hal 6, Placebo 3	Fair

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Funding	Comments
Ballard, 2005 UK Quetiapine and rivastigmine Fair	General donations to Clive Ballard [first author] research programme and profits from previously completed commercially funded clinical trials with additional support from the Alzheimer's Research Trust.	
Street et al., 2000 US	Sponsored in part by Eli Lilly and Company; 11 of 13 authors employed by Lilly Research Laboratories; 10 authors are stockholders in Eli Lilly.	
Streim 2008	Bristol-Myers Squibb & Otsuka Pharmaceutical Co,, Ltd.	
Suh, 2004 South Korea	Financially supported by Janssen Korea, Seoul, Korea.	
Tariot, 2004 (poster) US	Not reported; one author from AstraZeneca	
Tariot, 2006 US, 47 sites stated as double-blind quetiapine vs. haloperidol vs. placebo Fair	AstraZeneca Pharmaceuticals LP	23-35% in each group were taking concomitant anxiolytic or hypnotic medications during study

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Yes	Yes	Yes; 10 point difference in favor of placebo for severe impairment battery (Sign NR)	Yes	Yes	Yes	Yes
Verhey, 2006 Netherlands, 6 sites Olanzapine vs. Haloperidol	Method not reported	Not reported	Numerical differences in baseline Alzheimer's disease and vascular dementia between haloperidol and olanzapine (32%/39% vs. 40%/23%); those in haloperidol arm had higher baseline CMAI and NPI scores compared to olanzapine (5.4 and 7 point difference).	Yes	Reported as double-blind, but not specified	Reported as double-blind, but not specified	Unclear (reported as 'capsules' in the methods section and 'tablets' in the results section)
Zeneca Pharmaceuticals 5077IL/0049	Method not reported	Method not reported	No Greater % delusional symptoms in haloperidol group	Yes	NR (described as double blind)	NR (described as double blind)	Yes
Zhong et al, 2004 (poster) US	Method not reported	Not reported	Yes	Yes	Yes	Not reported	Yes
Zhong, 2007 US, 53 centers quetiapine vs. placebo Fair	Yes, random block size of 8, random seed and treatment allocation ratios of 3:3:2	Unclear	Yes	Yes	unclear	unclear	Yes

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Attrition, yes Crossover, no Adherence, no Contamination, no	Potentially, greater loss to follow-up in tx groups, Sign NR Lost to Follow-up: RIS: 10 QUE: 8 Placebo: 1	Yes	No	Fair
Verhey, 2006 Netherlands, 6 sites Olanzapine vs. Haloperidol	Attrition, yes Crossover, no Adherence, yes per pill count (89-95%) Contamination, no	Differential, not reported (discontinuations given as total and not per arm) High, no (15.5%)	Yes but some scores were imputed per LOC while others were treated as missing. If data were missing they were imputed by calculating the mean of scores of the previous and next assessments. In cases of premature dropout, data were imputed per LOCF. If <30% data points were missing for the total CMAI, NPI, MMSE, and UKU score, the total of non-missing items were scaled up to the intended scale. If >30% were missing, the total of score was considered as missing.	Yes 1-patient was excluded because of too many missing data; no other information provided	Fair-Poor
Zeneca Pharmaceuticals 5077IL/0049	Yes, No, No, No	No/Yes	No 108/114 (94.7%) in ITT	Yes	Fair
Zhong et al, 2004 (poster) US	Attrition yes, others no	High	No	Yes	Poor
Zhong, 2007 US, 53 centers quetiapine vs. placebo Fair	Attrition, yes Crossover, no Adherence, no Contamination, no	Differential, no High, yes 35% did not complete the study, no differences between the groups	Yes, LOCF	No	Fair

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Funding	Comments
Ballard, 2005 UK Quetiapine and rivastigmine Fair	General donations to Clive Ballard [first author] research programme and profits from previously completed commercially funded clinical trials with additional support from the Alzheimer's Research Trust.	
Verhey, 2006 Netherlands, 6 sites Olanzapine vs. Haloperidol	Not reported	unclear if 3-day washout was adequate since the authors did not report what previous meds the patients were on; baseline differences in diagnoses and CMAI, NPI scores; unclear how some data points were counted; did not address if any patients were taken out of the study due to intolerable side-effects and tx under open conditions
Zeneca Pharmaceuticals 5077IL/0049		
Zhong et al, 2004 (poster) US	Supported by AstraZeneca	
Zhong, 2007 US, 53 centers quetiapine vs. placebo Fair	AstraZeneca Pharmaceuticals	High number of participants on concomitant medications; short follow-up

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	N	Duration	Study design Setting	Eligibility criteria
Olanzapine vs. haloperidol				
Moretti, 2005 (FAIR)	346	12 months	Open-label, non-randomized controlled trial	Men and women, age 71-92 years with MMSE scores of at least 14 and satisfying DSM-IV criteria for dementia. Probable vascular dementia according to NINDS-AIREN criteria.
Quetiapine vs. haloperidol				
Savaskan, 2006 Switzerland (POOR)	22	5 weeks	Open-label, randomized, single center; inpatients	Confirmed diagnosis of Alzheimer's disease, behavioral symptoms (at least 3 of the following: aggression, psychotic symptoms, sleep-wake cycle disturbances, agitation, restlessness or sundowning), permanent medical or social care available during the study, written informed consent and over age 65.
Tariot, 2006: full publication (Replaces Tariot 2004, previously available as a poster only) (FAIR)	284	10 weeks	Double-blind, multicenter, 47 nursing homes	Men and women, age 65 and older, not bedridden, residing in nursing homes for at least 2 weeks; DSM-IV diagnosis of dementia or National Institute of Neurological and Communicative Disorders & Stroke-Alzheimer's Disease (NINCDS) diagnosis of Alzheimer's Disease; BPRS score 24 or higher, CGI-Severity score 4 or higher.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Exclusion criteria	Interventions (drug, dose)	Run-in/washout period
Olanzapine vs. haloperidol			
Moretti, 2005 (FAIR)	Signs of normal pressure hydrocephalus; previous psychiatric illness or CNS disorders, alcoholism	Olanzapine 2.5-7.5 mg/day; mean dose 4.23 mg/day (SD 2.12) Typical antipsychotics: promazine 4%, up to 10 drops tid; mean dose 1.65 mg/day (SD 0.23) or haloperidol 0.2%, up to 10 drops tid; mean dose 1.65 mg (0.23	One week to discontinue benzodiazepines or other neuroleptics
Quetiapine vs. haloperidol			
Savaskan, 2006 Switzerland (POOR)	Known sensitivity to study drugs, evidence of chronica and/or severe renal, hepatic, cardiovascular, pulmonary of gastrointestinal impairment or cancer, other antipsychotic medication than the study drugs, participation in any other drug trial and contraindications as detailed in the country-specific prescribing information for the study drugs.	Quetiapine mean dose 125 mg Haloperidol mean dose 1.9 mg	Maximum 7-day run-in period (not described)
Tariot, 2006: full publication (Replaces Tariot 2004, previously available as a poster only) (FAIR)	Other clinically significant medical conditions, history of drug-induced agranulocytosis, acute orthostasis, clinically significant abnormal electrocardiogram, or concurrent other Axis I DSM-IV diagnosis.	quetiapine: median of mean daily dose 96.9 mg; maximum 125.0 mg haloperidol: median of mean daily dose 1.9 mg; maximum 2.0 mg	No placebo run-in; antipsychotics discontinued for at least 48 hours.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Olanzapine vs. haloperidol			
Moretti, 2005 (FAIR)	Allowed to continue previous therapy (e.g., cholinesterase inhibitors, antihypertensive, antidyslipidemic, antidiabetic drugs)	Mean age 76.78 (SD 4.01) 44.4% female Race/ethnicity not reported	Subcortical vascular dementia: 11.6% Multi-infarct dementia: 88.4%
Quetiapine vs. haloperidol			
Savaskan, 2006 Switzerland (POOR)	Concomitant medication was continued and documented. All patients received a cholinesterase inhibitor (galantamine 2 X 8 mg)	Mean age 82 68.2% female Race/ethnicity not reported	All had Alzheimer's Disease, no prior history of psychiatric diagnosis
Tariot, 2006: full publication (Replaces Tariot 2004, previously available as a poster only) (FAIR)	Psychotropics permitted: chloral hydrate, zolpidem, lorazepam for sleep/agitation; anti-EPS medication (but not prophylactically), cholinesterase inhibitors if stable dose for >6 weeks prior to entry.	Mean age 83.9 73% female 89% white, 8% black, 2% Hispanic, <1% Asian.	100% Alzheimer's dementia

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures	Method of outcome assessment and timing of assessment
Olanzapine vs. haloperidol				
Moretti, 2005 (FAIR)	NR/NR/346	0/0/346	Clinical Dementia Rating Scale NPI Barthel Index Instrumental ADL Tinetti scale for equilibrium/balance and gait Cumulative Illness Rating Scale Hachinski Ischemic score Matthew's Stroke Scale Caregiver Burden Inventory	Hachinski Ischemic score and Matthew's Stroke Scale at first and last visit, others at every visit
Quetiapine vs. haloperidol				
Savaskan, 2006 Switzerland (POOR)	NR/NR/30	4/0/22	NPI Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery Nurses' Observation Scale for Geriatric Patients (NOSGER)	Baseline during run-in, 1 day prior to commencing study drugs, and end of week 5
Tariot, 2006: full publication (Replaces Tariot 2004, previously available as a poster only) (FAIR)	501/378/284	104 withdrawn/1 lost to followup/265 analyzed	BPRS- Total score, agitation factor subscale (tension, hostility, uncooperativeness, and excitement items) and anergia factor subscale (emotional withdrawal, motor retardation, blunted affect, disorientation) CGI-S CGI-C NPI-NH Agitation + Hallucinations + Delusions (NPI-3) MMSE Multidimensional Observation Scale for Elderly Subjects (MOSES) Physical Self-Maintenance Scale (PSMS)	Screening, baseline, weeks 2, 4, 6, and 10

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Results	Method of adverse event assessment	Adverse events
Olanzapine vs. haloperidol			
Moretti, 2005 (FAIR)	Mean change from baseline, olanzapine vs typical antipsychotics Clinical Dementia Rating Scale: +0.4 vs +0.51 (NS) NPI: -12.1 vs -9.74 (NS) Barthel Index: -6.4 vs -13.45 (p<0.05) Instrumental ADL: -1.7 vs -2.4 (NS) TINETTI equilibrium: -1.3 vs -5.7 (<0.01) TINETTI gait: -2.7 vs -7.4 (<0.01) TINETTI total: -4.0 vs -13.1 (<0.01) Clinical Insight Rating Scale: +1.4 vs+2.7 (<0.05) Caregiver Burden Inventory: -10.2 vs +2.7 (<0.05)	Not reported	2 deaths in olanzapine group (1.15%: MI and pneumonia); 3 in haloperidol group (1.73%: pulmonary embolism, MI, fracture complications) Olanzapine group: 5 new angina pectoris (2.89%), 2 (1.15%) diagnosed with diabetes, 1 peripheral arteriopathy, 1 renal failure, 1 fall. Haloperidol group: 4 (2.31%) angor episodes, 2 (1.15%) MI, 3 (1.73%) diagnosed with diabetes, 13 falls Mean weight increase: olanzapine: 5.65 kg (SD 1.45) haloperidol: 4.89 kg (SD 2.32)
Quetiapine vs. haloperidol			
Savaskan, 2006 Switzerland (POOR)	Results reported graphically only NPI: similar effects for both treatment groups for delusions and agitation. CERAD: both groups improved in word recall MMSE: no significant differences from baseline NOSGER: quetiapine improved instrumental ADL	Not reported	quetiapine: 1 discontinuation for postural hypotonia and 1 for MI haloperidol: 1 discontinuation for EPS and 1 for TIA Other adverse events: quetiapine: 1 reversible syncope, 1 gastroenteritis haloperidol: 1 infection of unknown origin, 1 arterial hypertonia
Tariot, 2006: full publication (Replaces Tariot 2004, previously available as a poster only) (FAIR)	All drug treatment groups improved from baseline to LOCF on BPRS total score and on the NPI-3 (Data presented graphically only) Quetiapine group had statistically significantly better functional status as assessed by the MOSES, PSMS, AND BPRS anergia factor compared with haloperidol (comparison to placebo not reported, data presented graphically only) Quetiapine and haloperidol groups had significantly more improvement than placebo patients on the BPRS agitation subscale (change from baseline, quetiapine -2.4 [p=0.033], haloperidol -2.9 [p=0.001], placebo -1.1) Quetiapine patients' scores on MMSE not significantly different from placebo; haloperidol results not reported.	Simpson-Angus Scale and AIMS at baseline, weeks 2, 4, 6, 8, and 10.	Withdrawals due to AEs: 11% quetiapine 18% haloperidol 13% placebo AEs with >10% incidence of which were statistically significantly different from placebo: somnolence, infection, rash, pain, conjunctivitis, vomiting, headache, cough increased, postural hypotension, dizziness, weight gain, weight loss, accidental injury. Of treatment-emergent adverse events, somnolence occurred statistically more often for quetiapine and haloperidol than for placebo.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	N	Duration	Study design Setting	Eligibility criteria
Zeneca Pharmaceuticals (5077IL/0049)	114	6 weeks	DB RCT Multicentre (18 centres)	Male or female, aged 65 years or over; satisfaction of the ICD-10 research diagnostic criteria for dementia in Alzheimer's disease, with the presence of predominantly delusional or hallucinatory symptoms; a score of at least 3 (mildly ill) on the CGI-S item; a score between 10 and 26 from the Mini Mental State Examination.
Risperidone vs. haloperidol				
Chan et al, 2001 Hong Kong (FAIR)	58	12 weeks	Double-blind, multicenter (3 centers)	Age 55 or older and met DSM-IV criteria for Dementia of Alzheimer's Type with behavioral disturbance, vascular dementia with behavioral disturbance or a combination of the two. Active behavioral symptoms, as evidenced by a frequency score of at least 4 on one and at least 3 on another item of the Cohen-Mansfield Agitation Inventory (CMAI). Symptoms present for at least 2 weeks. Score of at least 8 on Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD).

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Exclusion criteria	Interventions (drug, dose)	Run-in/washout period
Zeneca Pharmaceuticals (5077IL/0049)	Evidence of any significant clinical disorder or laboratory finding for this age group; patients with a history or clinical evidence on ECG of myocardial infarction within the last 3 months, or any clinically significant ECG result; total white blood cell count less than the lower limit of the reference range of the laboratory used for hematological monitoring; history of drug-induced agranulocytosis; satisfaction of diagnostic criteria for delirium superimposed on dementia.	Quetiapine (50, 75, 100, 200, or 300 mg/day) or haloperidol (1, 1.5, 2, 4, or 6 mg/day)	NR
Risperidone vs. haloperidol			
Chan et al, 2001 Hong Kong (FAIR)	No additional	risperidone 0.5 mg vs haloperidol 0.5 mg to start. Titrated by increments of 0.5 mg no faster than every other day. Target dose 1 mg per day, could be stepped up to 2 mg per day if symptoms poorly controlled.	7- to 14-day washout during which all psychotropic and antiparkinsonian drugs were stopped.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Zeneca Pharmaceuticals (5077IL/0049)	NR	77.7% are >75 years old 75.9% female 99.1% Caucasian	Quetiapine vs haloperidol late onset dementia: 83.6% vs 78.9% Alzheimer's Disease Assessment Scale: 30.8 vs 28.7 CGI-S: 4 vs 3.9
Risperidone vs. haloperidol			
Chan et al, 2001 Hong Kong (FAIR)	Medications permitted not reported, but report patients taking benzodiazepines (4 haloperidol, 4 risperidone), chloral hydrate (1 risperidone), benzhexol (2 haloperidol), donepezil (1 haloperidol), and donepezil (1 haloperidol).	Mean 80.5 (sd 8.2) 72% female 100% Chinese	79% Alzheimer's dementia, 21% vascular dementia

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures	Method of outcome assessment and timing of assessment
Zeneca Pharmaceuticals (5077IL/0049)	140/NR/114	34/NR/108	Neuropsychiatric Inventory, MADRS, CGI Severity of Illness, and Mini Mental State Examination, Cognitive assessments using the Alzheimer's Disease Assessment Scale, CGI Global Improvement (Day 42)	Baseline, Day 15 and Day 42
Risperidone vs. haloperidol				
Chan et al, 2001 Hong Kong (FAIR)	Number screened, eligible not reported, 58 enrolled	3 withdrew (1 haloperidol, 2 risperidone), 55 analyzed.	CMAI total score, BEHAVE-AD subscale scores, Functional Assessment Staging Rating Scale (FAST), Cantonese version of Mini-Mental State Examination (CMMSE).	Baseline, weeks 4, 8, and 12. Additional CMAI ratings at weeks 2, 6, and 10.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Results	Method of adverse event assessment	Adverse events
Zeneca Pharmaceuticals (5077IL/0049)	No differences between both groups in changes in Neuropsychiatric Inventory and MADRS total scores (*P*=0.156 and *P*=0.065 respectively)	SAR-S at baseline and at Days 15 and 42; the use of anticholinergic medication to treat EPS and adverse events related to EPS were recorded; all adverse events, and routine clinical laboratory tests, vital signs measurements, and ECGs were also performed.	Quetiapine vs haloperidol n(%) Death: 3 (5.6) vs 1 (1.8) Withdrawals due to AEs: 9 (16.7) vs 11 (19.6) No statistically significant differences between groups in proportion of patients developing clinically significant EPS (*P*=0.598), who experienced AEs related to EPS (*P*=0.447), and who received anticholinergic mediation to treat EPS (*P*=0.254) No clinically significant changes in laboratory data, blood pressure or pulse rate
Risperidone vs. haloperidol			
Chan et al, 2001 Hong Kong (FAIR)	Mean change from baseline to endpoint, risperidone vs haloperidol CMAI total: -8.1 vs -10 (p=0.95) BEHAVE-AD (Psychosis): -1.1 vs -0.6 (p=0.91) BEHAVE-AD (Activity disturbances): -0.8 vs -0.7 (p=0.16) BEHAVE-AD (Aggressiveness): -1.3 vs -1.3 (p=0.56) BEHAVE-AD (Diurnal rhythm disturbances): -0.4 vs -0.3 (p=0.36) BEHAVE-AD (Affective disturbances): -0.2 vs 0 (p=0.11) BEHAVE-AD (Anxieties and phobia): 0 vs -0.1 (p=0.19)	AIMS, Simpson-Angus Extrapyramidal Symptoms Scale, Barnes Akathisia Scale	Withdrawals due to Aes:0 risperidone; 3% haloperidol (somnolence) risperidone: no significant increase from baseline on Simpson-Angus, Barnes, or AIMS. haloperidol: significant increase in Simpson-Angus Scale (p<0.001)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	N	Duration	Study design Setting	Eligibility criteria
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	344	12 weeks	Double-blind, placebo-controlled, multicenter	Age 55 or older, institutionalized, diagnosis of primary degenerative dementia of the Alzheimer's type, vascular dementia, or mixed dementia according to the DSM-IV. Scores of 4 or greater on Functional Assessment Staging (FAST); 23 or greater on Mini-Mental Status Examination (MMSE); 1 or greater on the BEHAVE-AD global rating; and 8 or greater on the BEHAVE-AD total score.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Exclusion criteria	Interventions (drug, dose)	Run-in/washout period
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	Other conditions that diminish cognitive function; other psychiatric disorders; clinically relevant organic or neurologic disease; ECG or laboratory abnormalities; administration f a depot neuroleptic within one treatment cycle of Visit 1; history of allergic reaction to neuroleptics or history of neuroleptic malignant syndrome; participation in clinical trial(s) with investigational drugs during the 4 weeks preceding this trial.	risperidone 0.5 mg vs haloperidol 0.5 mg to start. Titrated by increments of 0.5 mg every 4 days if indicated, to 2 mg. Could be increased up to 4 mg per day if symptoms poorly controlled and no EPS.	1-week single-blind washout phase during which all psychotropic medications were discontinued.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Allowed other medications/interventions	Age Gender Ethnicity		Other population characteristics (diagnosis, etc)
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	Use of antipsychotics, antidepressants, lithium, carbamazepine, and valproic acid not permitted. Lorazepam permitted if limited to 4 days per week for the first 4 weeks of treatment. If needed beyond week 4, patient discontinued from study.	Mean 81 (range 56-97) 56% female 99% white, <1% black, Asian	<1%	74% Alzheimer's dementia, 33% Vascular Dementia (7% had both diagnoses)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures	Method of outcome assessment and timing of assessment
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	Number screened not reported/371 eligible/344 enrolled (27 dropped out during washout)	344 analyzed	BEHAVE-AD, Cohen-Mansfield Agitation Inventory (CMAI), and Clinical Global Impression (CGI)	Evaluations at selection, baseline, weeks 1, 2, 4, 6, 8, 10, 12.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Results	Method of adverse event assessment	Adverse events
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	Mean change from baseline to endpoint, risperidone vs haloperidol vs placebo BEHAVE-AD (Total): -5.2 vs -6.6 vs -4.2 BEHAVE-AD (Aggressiveness): -1.7 vs -1.6 vs -0.8 CMAI (Total aggressive): -3.9 vs -3.3 vs -1.6 CMAI (Physical aggressive): -2.7 vs -2.3 vs -0.7 CMAI (Verbal aggressive): -1.2 vs -1.0 vs -0.8 (No significant differences between risperidone and haloperidol) Mean change from baseline to week 12, risperidone vs haloperidol vs placebo BEHAVE-AD (Total): -8.6 vs -7.5 vs -6.2 (p NS for risperidone vs haloperidol) BEHAVE-AD (Aggressiveness): -2.9 vs -1.8 vs -1.5 (p=0.05 for risperidone vs haloperidol; post hoc analysis) CMAI (Total aggressive): -8.3 vs -3.6 vs -4.9 (p=0.02 for risperidone vs haloperidol; post hoc analysis) CMAI (Physical aggressive): -5.9 vs -2.8 vs -3.5 (p NS for risperidone vs haloperidol) CMAI (Verbal aggressive): -2.5 vs -0.8 vs -1.4 (p=0.01 for risperidone vs haloperidol; post hoc analysis)	Extrapyramidal Symptom Rating Scale	Withdrawals due to AEs: 18% total, no significant differences between groups. Mean change in Extrapyramidal Symptoms Rating Scale score: risperidone 0.5 to 2 mg: -0.3 haloperidol 0.5 to 2 mg: +1.6 placebo: -1.4 (p <0.05 for risperidone vs haloperidol, NS for risperidone vs placebo)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	N	Duration	Study design Setting	Eligibility criteria
Suh et al, 2004 South Korea (FAIR) Suh 2006 [post hoc analyses]	120	18 weeks (1 week washout, 8 weeks active treatment, 1 week washout, 8 weeks crossover treatment)	Double-blind, crossover, single center	Age 65 or older, diagnosis of dementia of the Alzheimer's type with behavioral disturbance, vascular dementia with behavioral disturbance, or a combination of the two, according to DSM-IV criteria. Score of 4 or higher on the Functional Assessment Staging Test, a total score of 8 or higher on the Korean version of the BEHAVE-AD, and a score of more than 3 on any two items of the Korean version of the CMAI.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Exclusion criteria	Interventions (drug, dose)	Run-in/washout period
Suh et al, 2004 South Korea (FAIR) Suh 2006 [post hoc analyses]	Other conditions that diminish cognitive function (e.g., Lewy-body dementia, hypothyroidism), other psychiatric disorders that might contribute to the psychotic symptoms (e.g., schizophrenia, delusional disorder), clinically relevant organic or neurologic disease, unstable medical conditions (e.g., poorly controlled hypertension, angina, or diabetes), abnormal electrocardiograms as diagnosed by a cardiologist or laboratory tests, a history of allergic reaction to antipsychotic treatment, and a history of neuroleptic malignant syndrome.	risperidone or haloperidol 0.5 mg to 1.5 mg (target dose was 1 mg). Dose could be titrated up or down; dosing regimen and intervals between dose titrations were individualized for each patient.	1-week washout period during which all psychotropic medications were discontinued.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Suh et al, 2004 South Korea (FAIR) Suh 2006 [post hoc analyses]	Concomitant use of antipsychotic drugs, antidepressants, and mood stabilizers was not permitted. Lorazepam permitted if limited to 4 days/week for the first 4 weeks of treatment.	Mean age 80.9 (SD 8.2, range 65-97) 80% female Ethnicity not reported (trial conducted in South Korea)	65.8% Alzheimer's dementia 28.3% vascular dementia 5.8% mixed

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures	Method of outcome assessment and timing of assessment
Suh et al, 2004 South Korea (FAIR) Suh 2006 [post hoc analyses]	280 screened/# eligible not reported/120 enrolled	6 withdrawn/0 lost to followup/114 analyzed	BEHAVE-AD-K, CMAI-K, AND CGI-C	Patients assessed weekly during the first 4 weeks and then every 2 weeks (twice) until the end of the final (8th week)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Results	Method of adverse event assessment	Adverse events
Suh et al, 2004 South Korea (FAIR) Suh 2006 [post hoc analyses]	Mean change from baseline to endpoint, risperidone vs haloperidol BEHAVE-AD-K (Total): - 7.2 vs - 4.7 (p=0.004) BEHAVE-AD-K (Psychosis): - 3.7 vs - 2.0 (p=0.582) BEHAVE-AD-K (Activity Disturbances) - 1.1 vs - 0.8 (p=0.858): BEHAVE-AD-K (Aggressiveness) - 1.1 vs - 0.9 (p=0.002) BEHAVE-AD-K (Diurnal Rhythm Disturbances): - 0.5 vs - 0.2 (p=0.038) BEHAVE-AD-K (Affective Disturbance): - 0.5 vs - 0.2 (p=0.248) BEHAVE-AD-K (Anxieties and Phobias): - 0.3 vs + 0.1 (p<0.0001) BEHAVE-AD-K (Wandering): - 0.3 vs + 0.1 (p<0.0001)* BEHAVE-AD-K (Agitation): - 0.3 vs + 0.1 (p<0.0001)* BEHAVE-AD-K (Godot syndrome): - 0.3 vs + 0.1 (p<0.0001)* BEHAVE-AD-K (Other anxieties): - 0.3 vs + 0.1 (p<0.0001)* CMAI-K (Total): - 14.2 vs - 5.9 (p<0.0001) CMAI-K (Aggressive Behavior): - 4.0 vs - 3.3 (p=0.001) CMAI-K (Physical Non-Aggressive Behavior): - 2.4 vs - 1.0 (p=0.024) CMAI-K (Verbally Agitated Behavior): - 1.1 vs - 0.5 (p=0.002) CMAI-K (Physical sexual advances): - 1.1 vs - 0.5 (p=0.002)* CMAI-K (Pace, aimless wandering): - 1.1 vs - 0.5 (p=0.002)* CMAI-K (Intentional falling): - 1.1 vs - 0.5 (p=0.002)* CMAI-K (Hoarding): - 1.1 vs - 0.5 (p=0.002)* CMAI-K (Performing repetitious mannerisms): - 1.1 vs - 0.5 (p=0.002)* CMAI-K (Repetitive sentence or questions): - 1.1 vs - 0.5 (p=0.002)* CMAI-K (Complaining): - 1.1 vs - 0.5 (p=0.002)* CMAI-K (Negativism): - 1.1 vs - 0.5 (p=0.002)* CGI-C: - 0.1 vs + 0.2 (p=0.001) *post hoc analysis from Suh 2006	All reported adverse events were recorded, and the severity of EPS was assessed by use of the ESRS.	Withdrawals due to AEs: 7% risperidone 3% haloperidol Mean change from baseline on ESRS, risperidone vs haloperidol: Total: +4.8 vs +13.8 (p=0.0001) Parkinsonism: +3.5 vs +10.4 (p=0.0001) Dystonia: +1.0 vs +2.5 (p=0.6503) Dyskinetic movement: +0.5 vs +0.9 (p=0.4144)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	N	Duration	Study design Setting	Eligibility criteria
Risperidone vs. citalopram				
Pollock 2007 USA	103	12 weeks	DB RCT Single center - University of Pittsburgh Medical Center	Dementia of the Alzheimer type (DAT), vascular dementia, dementia with Lewy bodies, mixed dementia, or dementia not otherwise specified.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Exclusion criteria	Interventions (drug, dose)	Run-in/washout period
Risperidone vs. citalopram			
Pollock 2007 USA	Current or past diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorders not otherwise specified, bipolar disorder, mental retardation, cognitive deficits following head trauma, or a current diagnosis of delirium, substance-induced persisting dementia, Parkinson disease, drug/alcohol abuse, or dependence; major depressive episode within the past 6 months or clinically significant depressive symptoms with a rating of 12 or higher on the Cornell Scale for Depression in Dementia ; unstable physical illness; creatinine 2.0 mg/100 mL; aspartate aminotransferase or bilirubin more than twice the upper limit of normal; potentially reversible cause of dementia; treatment with a depot neuroleptic drug within 2 months or fluoxetine within 4 weeks; or a history of allergy or intolerance to citalopram or risperidone.	Mean (SD) final doses Citalopram 29.4 (9.9) mg/day Risperidone 1.25 (0.51) mg/day	NR

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Risperidone vs. citalopram			
Pollock 2007 USA	Lorazepam and cholinesterase inhibitors or memantine	Citalopram vs. Risperidone Age (years) 82.0 (7.3) vs. 81.5 (9.2) Female, % (N) 47.2 (25) vs. 76.0 (38) White, % (N) 81.1 (43) vs. 82.0 (41)	Citalopram vs. Risperidone NBRS total score 60.3 (16.8) vs. 53.6 (15.6) NBRS agitation score 10.1 (4.8) vs.8.9 (4.5) NBRS psychosis score 5.9 (3.5) vs..6.0 (4.5) UKU total score 13.7 (5.2) vs..12.1 (4.1)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures	Method of outcome assessment and timing of assessment
Risperidone vs. citalopram				
Pollock 2007 USA	408/111/105	58/0/103	NBRS, CSDD, Neuropsychiatric Inventory (NPI), Udvalg for Kliniske Undersogelser (UKU) side effect scale, Mini-Mental State Examination (MMSE), Severe Impairment Battery (SIB), and Cumulative Illness Rating Scale–Geriatrics	Assessed at the time of enrollment; baseline ; after receiving study medication for 3 days, 7 days, then weekly for 5 weeks, then every 2 weeks; and at the time of discharge from the hospital or termination if the study was terminated early.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Results	Method of adverse event assessment	Adverse events
Risperidone vs. citalopram			
Pollock 2007 USA	Citalopram vs. Risperidone NBRS agitation score (items 8, 11, and 14) Post – pre 1.26 (4.58) 0.73 (4.91) P = 0.57 NBRS psychosis score (items 16, 18, and 20) Post – pre 1.90 (4.49) 2.16 (4.68) P = 0.79	UKU	Citalopram vs. Risperidone UKU total score Post – pre 0.49 (4.81) 2.33 (6.05) P = 0.011 UKU psychic subscale score Post – pre 0.91 (3.42) vs. 1.06 (3.77) P = 0.007 UKU neurologic subscale score Post – pre 0.15 (1.42) vs. 0.29 (2.36) P = 0.27 UKU autonomic subscale score Post – pre 0.02 (1.73) vs. 0.10 (2.34) P = 0.84 UKU other subscale score Post – pre 0.57 (1.08) vs. 0.76 (1.45) P = 0.46

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria
Olanzapine (oral)				
Street, 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	206	6 weeks	Double-blind, multicenter	Elderly nursing care facility residents, who met the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria for possible or probable Alzheimer's Disease. Score of 3 or higher on any of the Agitation/Aggression, Hallucinations, or Delusions items of the Neuropsychiatric Inventory- Nursing Home version (NH-NH) at screening and following placebo lead-in.
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	652	10 weeks	Double-blind, multicenter	Age 40 or older, resided in long-term nursing homes or continuing-care hospitals, and expected to continue patient status for 6 months following enrollment. Met NINCDS-ADRDA and DSM-IV - TR criteria for possible or probable Alzheimer's Disease, and exhibited clinically significant psychotic symptoms (delusions or hallucinations) that were (1) at least moderate in severity (i.e., impair functional capacity or cause them to pose a threat to themselves) at study entry and randomization; (2) present at least once per week for the month preceding study entry; and (3) require pharmacological intervention, in the opinion of the investigator. Minimum score of 5 on MMSE at Visit 1 and Visit 2.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Exclusion criteria	Interventions (drug, dose, duration)	Run-in/washout period
Olanzapine (oral)			
Street, 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	History of a DSM-IV Axis I disorder (e.g., schizophrenia, bipolar disorder, severe or recurrent depression), any neurological condition other than Alzheimer's disease that could contribute to psychosis or dementia, MMSE score of greater than 24, and bedridden status.	olanzapine 5 mg, 10 mg, or 15 mg	3- to 14-day single-blind placebo run-in; patients demonstrating a placebo response were not randomized.
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	Diagnosis of current primary mood disorder or other DSM-IV Axis I disorder with onset prior to diagnosis of Alzheimer's disease, including but not limited to schizophrenia, bipolar disorder, or delusional disorder.	olanzapine 1 mg, 2.5 mg, 5 mg, 7.5 mg, or placebo 10 weeks, fixed dose. Those assigned to 5 mg or 7.5 mg began at 2.5 mg and titrated to final dose by 2.5 mg per week increments.	Placebo run-in for up to maximum 14 days.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Olanzapine (oral)					
Street, 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	Benzodiazepines allowed as rescue medication but could not exceed 4 mg/day of lorazepam equivalents for a total of 21 days during the active treatment.	Mean age 83 years	Alzheimer's Disease	# screened not reported/288 eligible/206 enrolled	54 withdrawn/5 lost to followup/200 analyzed
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	Medications with primarily central nervous system activity were dis-allowed, except for the stable use of antidepressants, benzodiazepines, and acetylcholinesterase inhibitors. Use of anticholinergics for control of EPS was exclusionary. Limited use of benzodiazepines or hypnotics permitted with restrictions as a rescue medication to chronic users up to 4 mg/day	Mean age 77 (sd 10.4) 75% female 99.7% white	Mean baseline MMSE score 13.7 (sd 5.1); mean baseline NIP/NH Psychosis Total score 9.7 (sd 4.9)	Number screened, eligible not reported/652 enrolled	184 withdrawn/lost to followup not reported/642 analyzed

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Olanzapine (oral)		
Street, 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	Primary outcome measure: Neuropsychiatric Inventory-Nursing Home version (NH-NH) item scores for the core symptoms: Agitation/Aggression, Hallucinations, and Delusions. Secondary measures: NH/NH Total, Hallucinations and Delusions total (Psychosis Total), individual items, Occupational Disruptiveness score derived from the Agitation/Aggression, Hallucinations, and Delusions items (Core Disruptiveness), Brief Psychiatric Rating Scale total and subscale, MMSE	Assessments conducted at the nursing facility by neurologists, psychiatrists, geriatricians, psychometrists, nurses, and other medical specialists trained before study initiation. At screening, baseline, and end of study.
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	NH-NH Total NH-NH Psychosis CGI-C	Responses obtained by a trained interviewer from professional caregivers involved in the ongoing care of the patient in the previous week. Assessments weekly for the first 2 weeks of treatment and biweekly thereafter.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Results
Olanzapine (oral)	
Street, 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	**Mean change from baseline, Olanzapine vs placebo (p vs placebo):** **NPI/NH (Core Total)** 5 mg -7.6 (p<0.001); 10 mg -6.1 (p=0.006); 15 mg -4.9 (p=0.24); placebo -3.7 **NPI/NH (Occupational Disruptiveness)** 5 mg -2.7 (p=0.008); 10 mg -2.1 (p=0.28); 15 mg -2.3 (p=0.14); placebo -1.5 **NPI/NH (Agitation/Aggression)** 5 mg -4.1 (p=0.01); 10 mg -3.9 (p=0.02); 15 mg -3.1 (p=0.60); placebo -2.1 **NPI/NH (Psychosis Total)** 5 mg -3.6 (p=0.001); 10 mg -2.2 (p=0.04); 15 mg -1.9 (p=0.20); placebo -1.6 **NPI/NH (Hallucinations)** 5 mg -0.7 (p=0.007); 10 mg -0.2 (p=0.05); 15 mg -0.7 (p=0.10); placebo 0.0 **NPI/NH (Delusions)** 5 mg -2.9 (p=0.01); 10 mg -2.0 (p=0.15); 15 mg -1.3 (p=0.64); placebo -1.6 **NPI/NH (Depression/Dysphoria)** 5 mg -2.0 (p=0.28); 10 mg -0.6 (p>0.99); 15 mg -0.2 (p=0.32); placebo -1.0 **NPI/NH (Total)** 5 mg -18.7 (p=0.005); 10 mg -14.0 (p=0.09); 15 mg -9.7 (p=0.83); placebo -10.4 **BPRS (Total)** 5 mg -6.8 (p=0.005); 10 mg -5.6 (p=0.06); 15 mg -4.0 (p=0.13); placebo -1.4 **BPRS (Positive subscale)** 5 mg -2.0 (p=0.05); 10 mg -1.4 (p=0.40); 15 mg -1.4 (p=0.15); placebo -0.4 **BPRS (Anxiety/Depression subscale)** 5 mg -1.3 (p=0.04); 10 mg -1.5 (p=0.02); 15 mg -0.6 (p=0.29); placebo 0.1
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	NPI/NH, Mean change from baseline, Olanzapine vs placebo (p vs placebo): (Total): 1 mg -14.8 (p=0.547); 2.5 mg -15.7 (p=0.121); 5 mg -16.3 (p=0.199); 7.5 mg -17.7 (p=0.003); placebo -13.7 (Psychosis Total): 1 mg -6.0 (p<0.171); 2.5 mg -5.8 (p=0.089); 5 mg -5.6 (p=0.274); 7.5 mg -6.2 (p=0.032); placebo -5.0 (Agitation/Aggression): 1 mg -1.7 (p<0.039); 2.5 mg -1.7 (p=0.046); 5 mg -1.6 (p=0.70); 7.5 mg -2.0 (p=0.2002); placebo -1.3 (Anxiety): 1 mg -1.4 (p<0.658); 2.5 mg -1.5 (p=0.167); 5 mg -1.8 (p=0.43); 7.5 mg -1.7 (p=0.019); placebo -1.0 (Apathy/Indifference): 1 mg -1.0 (p<0.492); 2.5 mg -0.8 (p=0.174); 5 mg -0.8 (p=0.043); 7.5 mg -0.9 (p=0.612); placebo -1.1 (Delusions): 1 mg -4.3 (p<0.140); 2.5 mg -4.0 (p=0.071); 5 mg -4.2 (p=0.169); 7.5 mg -4.4 (p=0.002); placebo -3.6 (Euphoria/Elation): 1 mg -0.2 (p<0.391); 2.5 mg -0.3 (p=0.174); 5 mg -0.3 (p=0.43); 7.5 mg -0.5 (p=0.612); placebo -0.1 (Hallucinations): 1 mg -1.7 (p<0.150); 2.5 mg -1.8 (p=0.173); 5 mg -1.4 (p=0.852); 7.5 mg -1.7 (p=0.258); placebo -1.4 (Irritability/Lability): 1 mg -1.3 (p<0.154); 2.5 mg -1.3 (p=0.058); 5 mg -1.5 (p=0.007); 7.5 mg -1.6 (p=0.045); placebo -1.1 BPRS (Total): 1 mg -6.3 (p<0.405); 2.5 mg -8.7 (p=0.399); 5 mg -6.4 (p=0507); 7.5 mg -9.5 (p=0.23); placebo -6.9 BPRS (Negative): 1 mg -0.8 (p<0.342); 2.5 mg -0.9 (p=0.417); 5 mg -0.5 (p=0.122); 7.5 mg -0.5 (p=0.171); placebo -0.9 BPRS (Positive): 1 mg -2.8 (p<0.717); 2.5 mg -3.3 (p=0.167); 5 mg -2.6 (p=0.900); 7.5 mg -3.7 (p=0.21); placebo -2.7 CGI: 1 mg -3.1 (p<0.524); 2.5 mg -2.8 (p=0.030); 5 mg -2.9 (p=0.312); 7.5 mg -3.0 (p=0.2341); placebo -3.2

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Method of adverse event assessment	Adverse events
Olanzapine (oral)		
Street, 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	Simpson-Angus Scale, Barnes Akathisia Scale, AIMS	Withdrawals due to adverse events: 11% olanzapine 5 mg 8% olanzapine 10 mg 17% olanzapine 15 mg 4% placebo No statistically significant mean changes on Simpson-Angus Scale, Barnes Akathisia Scale, AIMS. Incidence of spontaneously reported EPS (tremor, hypertonia, cogwheel rigidity, hyperkinesia, akathisia, dyskinesia, dystonia, parkinsonism, tardive dyskinesia) was not significantly different from placebo. No differences between active treatment groups on any event
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	Simpson-Angus Scale, AIMS, mobility (gait and balance) measured with Modified Performance-Oriented Mobility Assessment-II (POMA); spontaneously reported treatment-emergent adverse events.	Withdrawals due to adverse events: 9.3% olanzapine 1 mg 6.7% olanzapine 2.5 mg 7.2% olanzapine 5 mg 9.8% olanzapine 7.5 mg 3.9% placebo Slight, non-significant improvement from baseline in each treatment group and placebo on AIMS and Simpson-Angus scales. Treatment-emergent abnormalities based on categorical analysis of the Simpson-Angus scale showed no overall differences among treatment groups (p=0.153), ranged from 15.6% in the placebo group to 4.7% in the olanzapine 1 mg group. No other assessments of treatment-emergent abnormal motor function were statistically significant, either on the Simpson-Angus scale, or AIMS. Deaths occurring during treatment or within 30 days after ending study participation: olanzapine 1 mg: 4 olanzapine 2.5 mg: 3 olanzapine 5 mg: 5 olanzapine 7.5 mg: 3 placebo: 2 Most frequent cause pneumonia, no deaths considered related to study medication.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria
Olanzapine (short-acting IM)				
Meehan, 2002 (Eli Lilly Study F1D-MC-HGHX) US, Russia, Romania (FAIR)	272	24 hours	Double-blind, multicenter; hospital inpatients or nursing homes	Male or female inpatients at least 55 years of age with a diagnosis of possible or probable Alzheimer's disease, vascular dementia, or mixed dementia. Score of 14 or above on the PANSS-EC, at least one individual PANSS item score 4 or higher, and be diagnosed with clinically significant agitation for which treatment with a parenteral agent was indicated.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Exclusion criteria	Interventions (drug, dose, duration)	Run-in/washout period
Olanzapine (short-acting IM)			
Meehan, 2002 (Eli Lilly Study F1D-MC-HGHX) US, Russia, Romania (FAIR)	Patients excluded if they received benzodiazepines, antipsychotics, or anticholinergics within 4 hours prior to the first injection of study drug, if they received psychostimulants or reserpine within one week prior to study drug administration, or an injectable depot neuroleptic within less than one dosing interval of study initiation, if they had been diagnosed with any serious neurological condition other than Alzheimer's disease or vascular dementia that cold contribute to psychosis or dementia, if they had laboratory or ECG abnormalities with clinical implications for the patient's participation in the study, or if they were judged to be at serious risk of suicide.	IM olanzapine 2.5 or 5 mg injection, given as 1, 2, or 3 injections over 24 hours	Not reported

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Olanzapine (short-acting IM)					
Meehan, 2002 (Eli Lilly Study F1D-MC-HGHX) US, Russia, Romania (FAIR)	Not reported	Mean age 77.6 years 92.3% white 61.0% female	% with dementia type not reported	331/NR/272 enrolled	20/0/272

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Olanzapine (short-acting IM)		
Meehan, 2002 (Eli Lilly Study F1D-MC-HGHX) US, Russia, Romania (FAIR)	PANSS-Excited Component CMAI Agitation-Calmness Scale PANSS-derived BPRS total CGI-Severity of Illness MMSE	2 hours and 24 hours post-injection

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Results
Olanzapine (short-acting IM)	
Meehan, 2002 (Eli Lilly Study F1D-MC-HGHX) US, Russia, Romania (FAIR)	Mean change from baseline to endpoint; olanzapine (p vs placebo) **PANSS-Excited Component at 2 hours** olanzapine 2.5 mg: -7.86 (p=0.024) olanzapine 5.0 mg: -8.67 (p=0.004) placebo:-5.27 **PANSS-Excited Component at 24 hours** olanzapine 2.5 mg: -6.44 (p=0.015) olanzapine 5.0 mg: -6.29 (p=0.024) placebo: -3.81 **CMAI at 2 hours** olanzapine 2.5 mg: -3.77 (p=0.090) olanzapine 5.0 mg:-3.97 (p=0.047) placebo: -2.78 **CMAI at 24 hours** olanzapine 2.5 mg: -2.82 (p=0.289) olanzapine 5.0 mg: -3.36 (p=0.056) placebo: -2.21 **Agitation-Calmness Scale at 2 hours** olanzapine 2.5 mg: 1.80 (p=0.013) olanzapine 5.0 mg: 1.88 (p=0.006) placebo: 1.04 **Agitation-Calmness Scale at 24 hours** olanzapine 2.5 mg: 0.90 (p=0.208) olanzapine 5.0 mg: 1.29 (p=0.003) placebo: 0.63 **PANSS-derived BPRS total at 24 hours** olanzapine 2.5 mg: -10.51(p=0.582) olanzapine 5.0 mg: -10.59 (p=0.560) placebo: -10.29 **PANSS-derived BPRS positive at 24 hours** olanzapine 2.5 mg: -1.72 (p=0.955) olanzapine 5.0 mg: -1.86 (p=0.906) placebo: -2.09 **CGI-Severity of illness at 24 hours** olanzapine 2.5 mg: -0.38 (p=0.347) olanzapine 5.0 mg: -0.47(p=0.647) placebo: -0.59

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Method of adverse event assessment	Adverse events
Olanzapine (short-acting IM)		
Meehan, 2002 (Eli Lilly Study F1D-MC-HGHX) US, Russia, Romania (FAIR)	Simpson-Angus Scale. Adverse events were detected by clinical evaluation and spontaneous report. ECGs recorded at screening and endpoint (2 and 24 hours post first injection and/or upon discontinuation after randomization)	No significant change from baseline to endpoint on SAS No withdrawals due to AEs Treatment-emergent AES not significantly different from placebo in any active-treatment group.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria
Quetiapine				
Ballard, 2005 UK (FAIR)	93	26 weeks	Double-blind, multicenter	People with dementia living in care facilities in Newcastle. Those with clinically significant agitation were referred by staff or physician; eligible if CMAI total score >39 and level of agitation was judged represent a clinically significant problem. Diagnosis of probable or possible Alzheimer's disease, age >60, clinically significant agitation for at least 6 weeks and scores of 4 or higher on the irritability or aberrant motor behavior scales of the neuropsychiatric inventory; and no use of antipsychotics or cholinesterase inhibitors for 4 weeks before entry into the study.
Zhong, 2007 Full publication, replaces Zhong 2004, previously available as a poster only US (FAIR)	333	10 weeks	Double-blind, multicenter	Diagnosis of dementia consistent with probable or possible Alzheimer's Disease (DSM-IV or NINCDS-ADRDA), vascular dementia (DSM-IV), or mixed dementia (DSM-IV) and clinical symptoms of agitation (Cohen-Mansfiled and Billig criteria) requiring treatment of antipsychotic medication in addition to behavioral intervention; Positive and Negative Syndrome Scale-Excitement Component (PANSS-EC) total score >14, one of the five items >4; residents in nursing homes or assisted living facilities >14 days.
Paleacu 2008 Israel	40	6 weeks	DB RCT in single center	age >50 years, dementia of the Alzheimer’s type diagnosed according to DSM-IV criteria, Mini-Mental State Examination (MMSE) score <24 and a score >6 on any of the Neuropsychological Inventory (NPI) items.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Exclusion criteria	Interventions (drug, dose, duration)	Run-in/washout period
Quetiapine			
Ballard, 2005 UK (FAIR)	Patients known to be sensitive to cholinesterase inhibitors or antipsychotics and those with advanced, severe, progressive, or unstable disease that might interfere with efficacy or put the patient at special risk; disability that might prevent them from completing study procedures; those with severe, unstable, or poorly controlled medical conditions; bradycardia (< 50), sick sinus syndrome, or conduction defects; current diagnosis of active uncontrolled peptic ulceration within the past three months; and clinically significant urinary obstruction.	quetiapine 50 mg twice daily rivastigmine 9 mg daily placebo Titrated up to week 26	NR
Zhong, 2007 Full publication, replaces Zhong 2004, previously available as a poster only US (FAIR)	History of schizophrenia, schizoaffective disorder or bipolar disorder, agitation that was judged not to be related to dementia, failure to respond to a prior adequate trial of atypical antipsychotics for the treatment of agitation, and unstable medical illness (included but not limited to cardiovascular, renal, hepatic, hematological, endocrine, cerebrovascular disorders, and abnormal ECG results). Psychotropic medications with few exceptions.	quetiapine 200 mg, quetiapine 100 mg or placebo.	Not reported
Paleacu 2008 Israel	other types of dementia (e.g. vascular, frontotemporal lobe dementia), concomitant malignant disease, active ischemic heart disease or chronic heart failure, women of childbearing potential and alcohol or drug abuse	Quetiapine median dose 200 mg vs. Placebo	2 week washout

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Quetiapine					
Ballard, 2005 UK (FAIR)	NR	Mean age 83.8 (SD 7.7) 79.6% female Race/ethnicity NR	All had Alzheimer's Disease	282/239/93	27/8/81
Zhong, 2007 Full publication, replaces Zhong 2004, previously available as a poster only US (FAIR)	Permitted antidepressants, hypnotics, benzodiazepines, cholinesterase inhibitors on a stable dose; hypnotics for insomnia; and lorazepam <4 mg per day or equivalent for agitation up to day 14 as needed.	Mean age 83 (SD 7.5) 74% female 85% white	81% Alzheimer's dementia 9% vascular dementia 10% mixed dementia	Number screened, eligible not reported/ 333 enrolled	114 withdrawn/lost to followup not reported/# analyzed not clear
Paleacu 2008 Israel	Zolpidem	Mean age 82.2 (SD 6.4) 65% female	Placebo vs. quetiapine (SD) MMSE 14.3 (6.8) vs. 14.5 (6.3) AIMS 0.3 (1.0) vs. 0.9 (22, appears to be typo perhaps should be 2.2) SAS 14.2 (3.5) vs. 15.8 (5.8)	44/40/40	13/1/40

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Quetiapine		
Ballard, 2005 UK (FAIR)	CMAI Severe Impairment Battery	Blinded assessment at baseline, 6, and 26 weeks
Zhong, 2007 Full publication, replaces Zhong 2004, previously available as a poster only US (FAIR)	PANSS-EC (Excitement Component) CGI-C	Not reported
Paleacu 2008 Israel	NPI, CGI-S, MMSE, SAS, AIMS	NPI score performed at entry, Weeks 4 and 6 and the Clinical Global Impression of Change score at entry, Weeks 2, 3, 4, 5, 6 and study end or withdrawal, MMSE score performed at study entry and end, the Simpson-Angus Scale and the Abnormal Involuntary Movement Scale entry and Weeks 2, 4, 6 and end

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Results
Quetiapine	
Ballard, 2005 UK (FAIR)	Mean change from baseline in CMAI , quetiapine vs placebo, mean difference (95% CI; p-value) Week 6: 3.5 (-3.7 to 10.8; p=0.3) Week 26: 2.0 (-4.2 to 8.3; p=0.5) Mean change from baseline in Severe Impairment Battery, quetiapine vs placebo, mean difference (95% CI; p-value) Week 6: -14.6 (-25.3 to -4.0; p=0.009) Week 26: -15.4 (-27.0 to -3.8; p=0.01)
Zhong, 2007 Full publication, replaces Zhong 2004, previously available as a poster only US (FAIR)	Least squares mean change from baseline (SE; p-value vs placebo for effect size) quetiapine 200 mg vs quetiapine 100 mg vs placebo PANSS-EC Total score: -5.7 (0.9; p=0.065) vs -4.9 (0.8; p=0.306) vs -3.9 (0.9) CGI-C: 3.0 (0.2; p=0.017) vs 3.2 (0.2; p=0.228) vs 3.6 (0.2) NPI-NH Total: -9.7 (2.2; p=0.546) vs -8.9 (2.1; p=0.791) vs -8.2 (2.4) NPI-NH Agitation: -1.1 (0.5; p=0.745) vs -0.9 (0.5; p=0.467) vs -1.2 (0.5) NPI-NH Depression: -0.4 (0.5; p=108) vs -1.1 (0.5; p=0.009) vs 0.6 (0.5) NPI-NH Psychosis: -2.5 (0.9; p=0.985) vs -1.8 (0.8; p=0.464) vs -2.5 (0.9) NPI-NH Occupational disruptiveness: -3.6 (0.8; p=0.460) vs -2.8 (0.7; p=0.839) vs -3.0 (0.8) CMAI Total: -11.0 (2.1; p=0.352) vs -9.2 (2.0; p=0.877) vs -8.8 (2.3) CMAI Physically aggressive behavior: -3.7 (0.9; p=0.976) vs -3.2 (0.9; p=0.796) vs -3.8 (1.0) CMAI non-aggressive physical behavior: -4.0 (0.7; p=0.182) vs -4.1 (0.7; p=0.067) vs -2.9 (0.8) CMAI verbal aggression: -3.4 (0.8; p=0.111) vs -3.1 (0.8; p=0.942) vs -3.4 (0.8)
Paleacu 2008 Israel	Placebo vs. quetiapine Primary outcomes reported in graphs Decreases from baseline in NPI total score: 79% vs. 68.5% CGI-C score decreased P = 0.480 vs. P = 0.009 MMSE 14.9 (7.3) vs. 13.5 (6.8)

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Method of adverse event assessment	Adverse events
Quetiapine		
Ballard, 2005 UK (FAIR)	Not reported	Not reported
Zhong, 2007 Full publication, replaces Zhong 2004, previously available as a poster only US (FAIR)	Assessments included treatment-emergent adverse events, clinically significant changes in laboratory tests, ECGs, and vital signs. AEs recorded using MedDRA system of nomenclature and incidence rates tabulated by system organ class and preferred term. EPS assessed by the SAS and AIMS Falls assessed at each occurrence using a modified Hendrich Fall Scale	No differences between groups on overall adverse events, withdrawals due to AEs, or change from baseline on the AIMS, SAS, or MMSE 19 deaths occurred: 5.1% quetiapine 200 mg/day, 7.3% quetiapine 100 mg/day, and 3.3% placebo. Relative risk for death for quetiapine vs placebo: 2.08 (95% CI 0.61, 7.16).
Paleacu 2008 Israel	At each visit patients were questioned regarding side effects and if reported these were recorded on a separate sheet and assessed as related or not to the medication and which measures were taken in consequence.	Placebo vs. quetiapine Akathisia 1 vs.. 0 Parkinsonism 1 vs. 1 Tremor 1 vs. 0 Diarrhea 1 vs. 0 Dizziness 1 vs. 0 Dry mouth 0 vs. 1 Edema 1 vs. 0 Falls 2 vs. 0 Headaches 0 vs. 1 Sedation 0 vs. 1 Confusion UTI 0 vs. 1 All 8 vs. 5 AIMS 0.2 (0.9) vs. 0.8 (2.2) SAS14.4 (3.0) vs. 16.1 (4.9)

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria
Trials of Risperidone				
Brodaty, 2003 Frank, 2004 Australia and New Zealand Brodaty 2005 (subgroup analysis) (FAIR)	309	12 weeks	Double-blind, multicenter	Diagnosis of dementia with aggressive behaviors; dementia was of the Alzheimer's type, vascular dementia, or a combination of the two, according to DSM-IV. Age 55 or older, score of 4 or greater on FAST, and 23 or less on MMSE; at least a minimum aggression score on CMAI; residing in a nursing home for at least 1 month prior to enrollment.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Exclusion criteria	Interventions (drug, dose, duration)	Run-in/washout period
Trials of Risperidone			
Brodaty, 2003 Frank, 2004 Australia and New Zealand Brodaty 2005 (subgroup analysis) (FAIR)	Medical or neurologic conditions other than dementia that diminish cognitive function, other types of dementia, major depression within the last 6 months, other psychiatric disorders that could have accounted for observed psychotic disturbances, a history of tardive dyskinesia, clinically uncontrolled organic disease, clinically relevant laboratory abnormalities, administration of a depot neuroleptic within 2 treatment cycles, a history of neuroleptic malignant syndrome or an allergic reaction to neuroleptic drugs, history of failure to respond to risperidone treatment of at least 4 weeks' duration, and participation in clinical trial(s) with any investigational drugs during the 4 weeks preceding selection.	risperidone oral solution 1 mg/mL, or placebo solution. Started with 0.5 mL. In case of insufficient response, dosage adjusted by increments of .5 mL no faster than every other day. Dosing was flexible throughout treatment period according to patient response and investigator judgment. Maximum dose 2 mL daily, corresponding to 2 mg risperidone.	Maximum 7-day single-blind placebo washout period during which existing psychotropic medication was discontinued.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Trials of Risperidone					
Brodaty, 2003 Frank, 2004 Australia and New Zealand Brodaty 2005 (subgroup analysis) (FAIR)	Short-acting benzodiazepines allowed for treatment of insomnia, provided the dosage had been stable for at least 3 months.	Mean age 83 (se 0.58) 72% female Ethnicity not reported	58% Alzheimer's dementia 28% vascular dementia 13% mixed dementia	Number screened not reported/384 eligible/345 enrolled	101 withdrawn/lost to followup not reported/304 analyzed

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Trials of Risperidone		
Brodaty, 2003 Frank, 2004 Australia and New Zealand Brodaty 2005 (subgroup analysis) (FAIR)	CMAI total aggression subscale BEHAVE-AD CGI-S CGI-C MMSE FAST Secondary analysis: Modified Strain in Nursing Care Assessment Scale (M-NCAS)	CMAI and BEHAVE-AD at selection, baseline, and weeks 4 and 8, and endpoint (either week 12 or patients' last visit); nurses responsible for daily care of patients were interviewed by an experienced and trained research nurse who subsequently rated the scales. CGI-S and CGI-C evaluated at selection, baseline, weeks 1, 2, 3, 4, and 8 and endpoint by specifically trained raters and patients' primary caregivers. FAST and MMSE assessed at selection and week 12 (or last visit) M-NCAS completed by the nurse career of individual residents at baseline, 4 weeks, 8 weeks, and 12 weeks.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Results
Trials of Risperidone	
Brodaty, 2003 Frank, 2004 Australia and New Zealand Brodaty 2005 (subgroup analysis) (FAIR)	CMAI, Mean change from baseline, risperidone vs placebo (Total aggression): -7.5 vs -3.1 (p<0.001) (Physical aggression): -5.4 vs -2.8 (p=0.008) (Verbal aggression): -2.1 vs -0.2 (p<0.001) (Total non-aggression): -7.3 vs -2.8 (p=0.002) (Physical non-aggression): -4.3 vs -2.5 (p=0.71) (Verbal non-aggression) -3.0 vs -0.3 (p<0.001) BEHAVE-AD (Total): -6.8 vs -2.3 (p<0.001) (Psychotic symptom subtotal): -2.0 vs -0.7 (p=0.004) (Paranoid and delusional ideation): -1.4 vs -0.7 (p=0.015) (Hallucinations): -0.6 vs -0.0 (p=0.010) (Activity disturbances): -0.8 vs -0.4 (p=0.067) (Aggressiveness): -2.0 vs -0.5 (p<0.001) (Diurnal rhythm disturbances): -0.3 vs -0.2 (p=0.098) (Affective disturbance): -0.5 vs -0.2 (p=0.034) (Anxiety and phobias): -1.1 vs -0.4 (p=0.004) M-NCAS mean change from baseline to endpoint (analysis on subgroup of 279 patients): Risperidone vs placebo Attention seeking: 0.24 vs 0.09 (p<0.05) Autonomy: 0.09 vs 0.07 (NS) Difficulty: 0.34 vs 0.17 (p<0.05) Total Attitude Domain: 0.24 vs 0.12 (p<0.05) Affect: 0.26 vs 0.10 (NS) Job satisfaction: 0.26 vs 0.09 (p<0.05) Neediness: 0.25 vs 0.07 (p<0.05) Predictability: 0.30 vs 0.22 (NS) Self direction: 0.19 vs 0.11 (NS) Total Strain Domain: 0.25 vs 0.12 (p<0.05)

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Method of adverse event assessment	Adverse events
Trials of Risperidone		
Brodaty, 2003 Frank, 2004 Australia and New Zealand Brodaty 2005 (subgroup analysis) (FAIR)	Monitoring the presence and severity of EPS at each visit and ratings on the Extrapyramidal Symptom Rating Scale.	Withdrawals due to adverse events: 13.2% risperidone 8.2% placebo Mean change in Extrapyramidal Symptoms Rating Scale score: 0.5 to 2 mg: +0.7 placebo: +0.5 (p=0.407) CVAEs: 9% risperidone (5 stroke, 1 TIA) vs 1.8% placebo. 2 deaths from stroke in risperidone group.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	625	12 weeks	Double-blind, multicenter	Age 55 or older, residing in a nursing home or chronic disease hospital, DSM-IV diagnosis of Alzheimer's disease, vascular dementia, or a combination of the two, with scores of 4 or greater on the Functional Assessment Staging rating scale and 23 or lower on the MMSE. Total score of 8 or more and a global rating of 1 or more on BEHAVE-AD rating scale.
Mintzer, 2006 US (FAIR)	473	8 weeks	Double-blind, multicenter	Age 55 or older, with Alzheimer's disease, residents of nursing home s or long-term care facilities, and mobile (ambulatory, walked with assistance, or used a wheelchair independently). Met criteria for psychosis of Alzheimer's disease and were deemed to be in need of treatment with an atypical antipsychotic in accordance with OBRA guidelines. Scored 2 or higher on any item of the BEHAVE-AD Psychosis subscale and between 5 to 23 on a MMSE.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Exclusion criteria	Interventions (drug, dose, duration)	Run-in/washout period
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	Untreated reversible causes of dementia, medical or neurological conditions that diminish cognition, diagnosis of dementia related to infection with HIV or substance-induced persistent dementia, diagnosis of delirium or amnestic disorder, and psychiatric diagnosis that could have accounted for the observed psychotic disturbances.	risperidone 0.5 mg, 1 mg, or 2 mg per day. Doses for patients receiving 1 mg and 1 mg were adjusted during the first week in increments of 0.5 mg every 2 days.	Single-blind placebo washout of 3 to 7 days.
Mintzer, 2006 US (FAIR)	Patients excluded had recently been treated with neuroleptic injections, had other medical conditions that diminish cognition, or had other psychiatric disorders that produce psychotic symptoms. Patients with epilepsy, recent diagnoses or cancer (except nonmelanoma skin cancers), unstable medical conditions, changes in prescription medications 30 days before screening, or significant baseline laboratory or ECG abnormalities were also excluded.	Risperidone daily flexible dosage in 2 divided doses. Initiated at 0.50 mg and increased after 3 days to 1 mg. If inadequate clinical response by day 13, increased to 1.5 mg. Subsequent adjustments were allowed in patients who experienced adverse events. Minimum treatment dosage was 0.5 mg daily.	One-week placebo run-in to wash out previously used psychotropic medications. Run-in length reduced for patients not using psychotropic medications and those whose psychosis or agitation worsened.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	Use of antipsychotics, antidepressants, or mood stabilizers not allowed. Benztropine allowed to treat EPS. Lorazepam (up to 3 mg/day for up to 4 days in any 7-day period) could be given until the end of week 4. Use of chloral hydrate for insomnia was allowed at the lowest effective dose.	Mean age 82.7 (sd 7.7) 68% female 89% white, 11% multiracial	73% Alzheimer's dementia 16% vascular dementia 12% mixed	729 screened/625 eligible/625 enrolled	190/NR/617 analyzed
Mintzer, 2006 US (FAIR)	Lorazepam (maximum daily dose 1.0 mg) during the run-in phase and the first 4 weeks of treatment. Maximum daily dose of 0.5 mg 3 days per week.	Mean age 83.3 77% female 80.1% white, 10.1% black, 6.6% Hispanic, 2.1% Asian, 1.1% other	100% Alzheimer's dementia	560/NR/473	117/1/416

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	BEHAVE-AD, CMAI, CGI	Assessments at selection, baseline, and weeks 1-4, 6, 8, 10, and 12 (or when patient was terminated from treatment). Elicited from patients' primary caregivers by specifically trained raters.
Mintzer, 2006 US (FAIR)	BEHAVE-AD Psychosis (primary efficacy measure) CGI-C BEHAVE-AD: Activity disturbances, Aggressiveness, Diurnal rhythm disturbances, Affective disturbance, Anxieties and phobias, Total, Global Part 2.	BEHAVE-AD assessed at baseline and treatment weeks 1, 2, 4, and 8. CGI-Change determined at weeks 1, 2, 3, 4, 6, and 8, using baseline CGI-S as a reference point.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Results
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	Mean change from baseline to endpoint, risperidone vs placebo (p vs placebo): BEHAVE-AD (Total) 0.5 mg -4.8 (p.37); 1 mg -6.5 (p=0.002); 2 mg -6.4(p=0.001); placebo -4.2 BEHAVE-AD (Psychosis subscale) 0.5 mg -1.6 (p=0.68); 1 mg -2.5 (p=0.005); 2 mg -2.2 (p=0.01); placebo -1.5 BEHAVE-AD (Aggressiveness subscale) 0.5 mg -1.3 (p=0.11); 1 mg -1.7 (p=0.002); 2 mg -2.4 (p<0.001); placebo -0.9
Mintzer, 2006 US (FAIR)	N=416 Mean change from baseline to endpoint (SD), risperidone vs placebo (analysis of covariance model, including treatment group and site as factors and baseline score as a covariate): BEHAVE-AD (Psychosis): –2.9 (3.55) vs –2.3 (3.55) p=0.118 BEHAVE-AD (Activity disturbances): –0.4 (1.78) vs –0.6 (1.80) p=0.812 BEHAVE-AD (Aggressiveness): –1.1 (2.42) vs –1.0 (2.83) p=0.078 BEHAVE-AD (Diurnal rhythm disturbances): –0.2 (0.81) vs –0.2 (3.55) p=0.643 BEHAVE-AD (Affective disturbance): –0.1 (1.19) vs –0.2 (1.11) p=0.199 BEHAVE-AD (Anxieties and phobias): –0.4 (1.67) vs –0.4 (1.49) p=0.943 BEHAVE-AD (Total): –4.9 (8.23) vs –5.0 (8.27) p=0.386 BEHAVE-AD (Global Part 2): –0.6 (0.91) vs –0.5 (0.97) p=0.111 CGI-C, risperidone vs placebo (controlling for site) Marked worsening: 4.0% vs 4.2% Moderate worsening: 6.0% vs 4.2% Minimal worsening: 5.5% vs 5.6% No change: 18.9% vs 30.0% Minimal improvement: 33.3% vs 21.6% Moderate improvement: 24.9% vs 23.0% Marked improvement: 7.5% vs 11.3% overall p=0.416

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Method of adverse event assessment	Adverse events
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	Information regarding adverse events was obtained at each visit, Extrapyramidal Symptom Rating Scale.	Withdrawals due to adverse events: 8% risperidone 0.5 mg 16% risperidone 1 mg 24% risperidone 2 mg 12% placebo Change from baseline to endpoint, Extrapyramidal Symptom Rating Scale scores (total and hypokinesia scales): risperidone 0.5 mg: -0.48 and 0.01 (NS vs placebo) risperidone 1 mg: 0.84 and 0.95 (NS vs placebo) risperidone 2 mg: 2.37 and 2.01 (p<0.001 vs placebo for both scales) placebo: -0.22 and 0.17 Tardive dyskinesia emerged in 1 placebo patient, 0 risperidone Deaths: 4% risperidone 0.5 mg; 9% risperidone 1 mg; 4% risperidone 2 mg; 3% placebo Serious adverse events: 11% risperidone 0.5 mg; 16% risperidone 1 mg; 18% risperidone 2 mg; 13% placebo
Mintzer, 2006 US (FAIR)	Simpson-Angus Scale, Barnes Akathisia Scale, AIMS	Withdrawals due to adverse events: quetiapine 200 mg: 12% quetiapine 100 mg: 7.3% placebo: 35%: 7.6% No significant difference in mean changes on SAS and AIMS among treatment groups (data not reported) Incidence of EPS-related adverse events: quetiapine 200 mg: 5% quetiapine 100 mg: 5% placebo: 4% Mean change in MMSE at end of treatment was 0 for all treatment groups. 1 transient ischemic attack in placebo group.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria
Aripiprazole				
Mintzer, 2007 Multinational	487	10 weeks	Double-blind, multicenter	Men and women aged 55–95 years (inclusive), who were diagnosed with AD and psychotic symptoms of delusions or hallucinations, who were living in nursing homes or residential assisted-living facilities for a minimum of four weeks ; capable of selflocomotion (alone or with the aid of an assistive device) and have an identified or proxy caregiver. MMSE score2 of 6–22 points (inclusive), and had experienced persistent or intermittent delusions, hallucinations or both for at least one month; presence of psychotic symptoms was confirmed by scores of 6 or higher on either the delusions or hallucinations items of the NPI-NH Psychosis Subscale score.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Exclusion criteria	Interventions (drug, dose, duration)	Run-in/washout period
Aripiprazole			
Mintzer, 2007 Multinational	an axis I diagnosis of delirium, amnestic disorder, bipolar disorder, schizophrenia or schizoaffective disorder, or mood disorder with psychotic features; non-AD; a current major depressive episode with psychotic symptoms of hallucinations or delusions; seizure disorders; history of refractoriness to antipsychotics; known hypersensitivity to aripiprazole or other quinolinones; suicidal ideation or history; unstable thyroid function; clinically significant abnormal laboratory findings; or previous participation in aripiprazole trials; were women who were pregnant or nursing or of childbearing potential and not using adequate contraception.	fixed doses of aripiprazole (2 mg/day, 5 mg/day, or 10 mg/day) or placebo for 10 weeks	7 day washout and 28 day screening period

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Aripiprazole					
Mintzer, 2007 Multinational	Lorazepam and anticholinergic medication for treating EPS, at a maximum dose equivalent to 2 mg/day of benztropine, stable doses of cholinesterase inhibitors or antidepressants at baseline	Mean age 82.5 79% female 87% white	100% Alzheimer's Disease	NR/NR/654	203/NR/475

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Aripiprazole		
Mintzer, 2007 Multinational	NPI-NH Total score and subscores Clinical Global Impression–Severity of Illness (CGI-S) score; BPRS Psychosis Subscale, Core and Total scores; CMAI Total score; MMSE score; and the mean CGI-I score	NPI-NH administered by caregiver, all others by investigators NPI-NH and CGI-S were performed at randomization (baseline), and at weeks 1, 2, 3, 4, 6, 8, and 10, CGI-I evaluations were performed at each time point except baseline. The BPRS and CMAI baseline, then every 2 weeks during the study. MMSE was carried out at screening and week 10.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Results
Aripiprazole	
Mintzer, 2007 Multinational	Placebo vs. Aripiprazole 2 mg vs Aripiprazole 5 mg vs. Aripiprazole 10 mg NPI-NH total mean change [2 x SD] 13.0 [32.8] vs. 14.1 [38.6] vs. 15.9 [37.2] vs 17.6[33.2] CGI-S mean change [2 x SD] 0.5 [1.6] vs. 0.5 [1.8] vs. 0.6 [1.8] vs. 0.7 [1.8] CGI-I (SD) 3.5 [2.8] vs. 3.3 [2.6] vs. 3.2 [2.8] vs. 3.2 [3.0] MMSE mean change [2 x SD] 0.9 [6.2] vs. 0.3 [6.2] vs. 1.6 [7.0] vs. 1.0 [7.4]

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Method of adverse event assessment	Adverse events
Aripiprazole		
Mintzer, 2007 Multinational	Medical review of adverse event reports, physical examination, vital sign measurements, and results of standard clinical laboratory tests and 12-lead electrocardiograms (ECGs). Extrapyramidal symptoms (EPS) were rated using the Simpson–Angus Scale, the Abnormal Involuntary Movement Scale and the Barnes Akathisia Rating Scale	Placebo vs. Aripiprazole 2 mg vs Aripiprazole 5 mg vs. Aripiprazole 10 mg n(%) Accidental injury 23 (19) vs. 35 (30) vs. 29 (24) vs. 25 (20) Agitation 20 (17) vs. 13 (11) vs. 9 (7) vs. 13 (11) Urinary-tract infection 16 (13) vs. 19 (16) vs. 23 (19) vs. 25 (20) Anorexia 13 (11) vs. 10 (9) vs. 6 (5) vs 7 (6) Ecchymosis 12 (10) vs. 10 (9) vs. 6 (5) vs. 11 (9) Edema, peripheral 10 (8) vs. 12 (10) vs. 7 (6) vs. 11 (9) Insomnia 10 (8) vs. 11 (9) vs. 7 (6) vs. 6 (5) Rash 10 (8) vs. 11 (9) vs. 11 (9) vs. 10 (8) Vomiting 8 (7) vs. 13 (11) vs. 11 (9) vs. 8 (7) Extremity pain 7 (6) vs. 8 (7) vs. 11 (9) vs. 12 (10) Skin ulcer 9 (8) vs. 12 (10) vs. 14 (12) vs. 11 (9) Diarrhea 7 (6) vs. 7 (6) vs. 8 (7) vs. 11 (9) Constipation 6 (5) vs. 6 (5) vs. 6 (5) vs. 4 (3) Coughing 6 (5) vs. 6 (5) vs. 4 (3) vs. 7 (6) Upper respiratory infection 6 (5) vs. 10 (9) vs. 6 (5) vs. 6 (5) Infection 5 (4) vs. 9 (8) vs. 6 (5) vs. 7 (6) Confusion 5 (4) vs. 3 (3) vs. 9 (7) vs. 6 (5) Headache 4 (3) vs. 5 (4) vs. 5 (4) vs. 9 (7) Back pain 4 (3) vs. 6 (5) vs. 4 (3) vs. 8 (7) Abdominal pain 4 (3) vs. 3 (3) vs. 8 (7) vs. 5 (4) Weight loss 4 (3) vs. 6 (5) vs. 6 (5) vs. 5 (4) Somnolence 4 (3) vs. 4 (3) vs. 12 (10) vs. 9 (7) Asthenia 3 (3) vs. 7 (6) vs. 11 (9) vs. 12 (10) Conjunctivitis 3 (3) vs. 7 (6) vs. 3 (2) vs. 3 (2) Urinary incontinence 2 (2) vs. 2 (2) vs. 12 (10) vs. 7 (6) Edema 2 (2) vs. 6 (5) vs. 4 (3) vs. 2 (2) Abnormal gait 1 (1) vs. 2 (2) vs. 9 (7) vs. 5 (4) Increased salivation 1 (1) vs. 2 (2) vs. 9 (7) vs. 2 (2) Lightheadedness 0 (0) vs. 6 (5) vs. 5 (4) vs. 4 (3) Cerebrovascular adverse events were reported for seven aripiprazole-treated patients during the study period (one in the 2 mg/day dose group, two in the 5 mg/day dose group and four in the 10 mg/day dose group), compared with no patients in the placebo group. EPS-related adverse events placebo, 6%; aripiprazole 2 mg/day, 8%; aripiprazole 5 mg/day, 7%; aripiprazole 10 mg/day, 7%).

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria
De Deyn, 2005 Multinational	208	10 weeks	Double-blind, multicenter	Noninstitutionalized men and women , aged 55–95 years, diagnosed with AD, and with symptoms of delusions or hallucinations present (at least intermittently) for 1 month or longer were eligible for enrollment in the study. MMSE score of 6–24, and a score of 6 on the delusions or hallucinations items of the Neuropsychiatric Inventory (NPI)20 assessment at baseline.
Streim 2008 United States	256	10 weeks	DB RCT Multicenter	Men and women aged 55–95 years , diagnosed with AD (DSM–IV criteria), and who had psychotic symptoms of delusions or hallucinations for 1 month, institutionalized for 4 weeks before study entry; capable of self-locomotion or locomotion with the aid of an assistive device; and have a caregiver or family member who could serve as a collateral informant for study assessments and, if necessary, provide proxy consent to participate. MMSE score between 6 and 22 at screening, and a score of 6 on either the delusions or hallucinations items of the Neuropsychiatric Inventory–Nursing Home Version (NPI-NH) at baseline (at the time of randomization).

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Exclusion criteria	Interventions (drug, dose, duration)	Run-in/washout period
De Deyn, 2005 Multinational	diagnosis of delirium, amnesic disorders, bipolar disorder, schizophrenia or schizoaffective disorder, or mood disorder with psychotic features; psychotic symptoms better accounted for by another general medical condition or direct physiologic effects of a substance (eg, medication); refractory to neuroleptics used to treat psychotic symptoms in the past.	Aripiprazole 2 mg/d (Aripiprazole could be titrated to higher doses (5, 10, and 15 mg/d) at 2-week intervals) or placebo, administered once-daily for 10 weeks,	7-day washout period for previous psychotropic medication
Streim 2008 United States	Axis I diagnosis of delirium or schizophrenia; a schizoaffective, mood, bipolar, or amnestic disorder; any reversible cause of dementia; continuous symptoms of psychosis before the onset of dementia; psychotic symptoms better accounted for by another medical condition or direct effects of a substance; a current episode of major depression with symptoms of psychosis; dementia resulting from vascular causes; any specific non-AD-type dementia caused by trauma, disease, infection, or substance abuse; a seizure disorder; and/or unstable thyroid pathology within the past 3 months; previously been refractory to antipsychotic drug treatment for psychosis; had been randomized in an aripiprazole clinical study; had participated in any clinical study with an investigational agent 1 month; recent treatment with a long-acting antipsychotic agent in which the last dose was administered 1 full cycle plus 1 week prior to randomization; met DSM–IV criteria for any significant substance use disorder; were deemed to be at significant risk of suicide; were likely to require prohibited concomitant therapy; were known to be allergic or hypersensitive to aripiprazole or quinolinones; had any laboratory test, vital sign, or ECG abnormalities that could indicate an elevated risk for significant adverse events (AEs), or any medical condition that would make study participation unsafe.	Placebo vs. Aripiprazole (2-15 mg, mean of 10 mg) for 10 weeks (there was early escape at 6 weeks)	7 day washout

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
De Deyn, 2005 Multinational	Zolpidem, anti-depressants, lorazepam, anticholinergic treatment of EPS	Mean age 81.5 72% female 98% white	100% Alzheimer's Disease	NR/NR/208	31/NR/208
Streim 2008 United States	trazodone 25–50 mg, zolpidem 2.5–5.0 mg or temazepam 7.5–15.0 mg analgesics or antipyretics , anxiolytics, cognition enhancers, and selective serotonin reuptake inhibitors	Mean age 83.0 24% male 89% white	83% delusional	NR/NR/330	105/0/249

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
De Deyn, 2005 Multinational	NPI-NH Total score and subscores Clinical Global Impression–Severity of Illness (CGI-S) score; BPRS , Core and Total scores; CMAI Total score; MMSE score;	NPI-NH administered by caregiver, others NR. Timing of assessments every two weeks following baseline.
Streim 2008 United States	NPI. CGI-S, CGI-I, BPRS, CMAI, CDS, MMSE	NPI-NH and CGI-S assessments were performed at randomization (baseline) and Weeks 1, 2, 3,4, 6, 8, and 10; CGI-I was evaluated at each time point except baseline. BPRS and CMAI were assessed at baseline, then every 2 weeks during the study. The Cornell depression scale was assessed at baseline and Weeks 6 and 10. MMSE was evaluated at screening and Week 10.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Results
De Deyn, 2005 Multinational	Placebo vs. aripiprazole NPI Psychosis mean change 5.52 vs. 6.55 P = 0.169 NPI Total mean change 9.75 vs. 11.20 P = 0.582 BPRS Psychosis mean change 1.27 vs. 1.93 P = 0.029 BPRS Core mean change 2.7 vs. 3.9 P = 0.042 BPRS Total mean change 6.58 vs. 8.53 P = 0.153 CGI-S mean change 0.54 vs. 0.69 P = 0.345 CGI-I 3.07 vs. 3.17 P = 0.564 MMSE mean change 0.53 vs. 0.81 P = 0.001
Streim 2008 United States	Placebo vs.. Aripiprazole (2*SD) NPI-NH Psychosis -4.62 (9.56) vs. -4.53 (9.23) P = 0.883 CGI-S 0.43 (1.65) vs. -0.57 (1.63) P = 0.198 NPI-NH total -10.01(37.66) vs. -16.43 (34.63) P = 0.009 BPRS Total –5.14 (17.76) vs. –7.73 (16.32) P = 0.031 BPRS Psychosis –1.24 (3.91) vs –1.18 (3.63) P = 0.823 BPRS Core –1.97 (6.80) vs. –2.48 (5.58) P = 0.231 CMAIa –6.16 (29.11) vs. –10.25 (25.70) P = 0.030 Cornell scale –0.13 (10.18) vs. –1.98 (8.25) P = 0.006 NPI-NH Total Caregiver distress –4.31 (14.37) vs. –7.23 (14.64) P = 0.003 NPI-NH Psychosis Caregiver distress –1.62 (3.27) vs. –1.89 (3.63) P = 0.246 MMSE –0.57 (6.34) vs. –0.77 (5.97) P = 0.685 ADCS-ADL-SEV –0.22 (9.03) vs. –0.83 (9.88) P = 0.442 CGI-I score at endpoint 3.65 (2.64) vs. 3.13 (2.35) P = 0.002 NPI-NH Total response 28% vs. 46% P = 0.006 NPI-NH Psychosis response 52% vs. 54% P = 0.959

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Method of adverse event assessment	Adverse events
De Deyn, 2005 Multinational	AE reports, extrapyramidal symptoms (EPS) rating scales, 12-lead ECGs, vital signs, and body weight measurements.	Serious AEs were reported by 25 patients (12%) during double-blind treatment or within 30 days of discontinuation (placebo, n = 9; aripiprazole, n = 16) EPS-related AEs (aripiprazole, n = 5; placebo, n = 4). Weight changes aripiprazole and placebo (+0.17 kg vs. 0.33 kg; P = 0.321), and clinically significant gain (7% increase in weight from baseline) at end point (aripiprazole, 5%; placebo, 3%; P = 0.695).
Streim 2008 United States	Medical review of AE reports, physical examination, vital sign measurements, standard clinical laboratory tests, and 12-lead ECGs. Extrapyramidal symptoms (EPS) were evaluated using the Simpson–Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS) and Barnes Akathisia Rating Scale (BAS).	Placebo vs.. Aripiprazole (%) Accidental injury 30 vs. 21 Agitation 12 vs. 8 Asthenia 7 vs. 12 Ecchymosis 13 vs. 12 Rash 12 vs. 10 Somnolence 4 vs. 14 Ulcer skin 12 vs. 9 Urinary tract infection 11 vs. 14 Vomiting 8 vs. 10 EPS-related AEs 4 vs. 5

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria
Intramuscular Aripiprazole				
Rappaport 2009 USA	129	24 hours	Double-blind, multicenter	Male and female patients (aged 55 to 95) diagnosed with AD, vascular, or mixed dementia, residing in healthcare facilities) who manifested moderate-to severe acute exacerbations of agitated behaviors defined as Positive and Negative Syndrome Scale (PANSS) Excited Component (PEC) score ≥ 15 and ≤ 32 with at least 1 of the 5 items with a score 4 or more.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Exclusion criteria	Interventions (drug, dose, duration)	Run-in/washout period
Intramuscular Aripiprazole			
Rappaport 2009 USA	Other major DSM-IV Axis I psychiatric disorders; those with a history of neuroleptic malignant syndrome, seizure, abnormal electroencephalogram not attributable to AD or vascular dementia, severe head trauma or stroke, and compulsorily detained patients.	Injection of IM aripiprazole (2.5, 5 or 10 mg) or IM placebo, followed by a second injection 2 hours later (2.5, 5 mg or placebo). Patients were clinically observed over 24 hours.	NR

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Intramuscular Aripiprazole					
Rappaport 2009 USA	Yes except medications that might have interfered with assessments of efficacy or safety were prohibited within 4 hours before baseline assessment and during the 4-hour efficacy evaluation phase after baseline.	Placebo vs. aripiprazole n = 26 vs. 103 % male 38 vs.35 % white 85 vs. 81 % black 25 vs. 19 % Hispanic 6 vs. 10	Placebo vs. aripiprazole Underlying diagnosis % Alzheimer's 85 vs.78 Mixed 8 vs. 15 Vascular 8 vs. 8	NR/NR/150	2/0/127

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Outcome scales	Method of outcome assessment and timing of assessment
Intramuscular Aripiprazole		
Rappaport 2009 USA	PEC, Agitation–Calmness Evaluation Scale (ACES), Clinical Global Impressions–Severity of Illness (CGI-S), and Clinical Global Impressions–Improvement (CGI-I)	Assessed at baseline 30 minutes, 1 hour, 1.5 hours, 2, 3, 4, 6, 12, 24 hours

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Results
Intramuscular Aripiprazole	
Rappaport 2009 USA	ACES increase from baseline Placebo vs. all aripiprazole 0.8 (0.1) vs.. 1.3 (0.1) All other comparisons are in graphs

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Counnry Trial name (Quality score)	Method of adverse event assessment	Adverse events
Intramuscular Aripiprazole		
Rappaport 2009 USA	AEs and changes in electrocardiograms, vital signs, laboratory tests, and the Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Mini Mental State Examination (MMSE)	Placebo vs. All aripiprazole n(%) Any AE 8 (32.0) vs. 56 (54.4) Somnolence 2 (8.0) vs. 37 (35.9) Dementia 0 vs. 3 (2.9) Lethargy 0 vs. 1 (1.0) Vomiting 0 vs. 4 (3.9) Pyrexia 0 vs. 1 (1.0) Skin laceration 2 (8.0) vs. 2 (1.9) Fall 1 (4.0) vs. 1 (1.0) Femoral neck fracture 0 vs. 1 (1.0) Electrocardiogram change 0 vs. 1 (1.0) Irregular heart rate 0 vs. 1 (1.0) Insomnia 0 vs. 3 (2.9) Agitation 2 (8.0) vs. 1 (1.0)

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Main outcome	Study design	Study objective
Barnett 2007	CVAEs	Prospective cohort	To examine the risk of a CVE in patients diagnosed with Alzheimer or vascular dementia while being treated with SGA, first-generation antipsychotics, or no antipsychotic medication
Finkel, 2005 US	CVAEs	Retrospective cohort	To determine whether risperidone is associated with an increased risk of cerebrovascular events relative to other commonly considered alternative treatments.

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Time period covered	Data source/ Inclusion criteria	Sample size	Population characteristics
Barnett 2007	June 2002-December 2003	Veterans Administration and Medicare Provider and Analysis Review Part A databases	14,029	Patients 65 years or older with dementia Mean age (y) = 77.5±5.5 Male (n, %) = 1548, 97.7 White (n, %) = 1355, 85.5 Alzheimer-dementia (n, %): 1234, 77.9 Vascular-dementia (n, %): 351, 22.1
Finkel, 2005 US	1999-2002	Medicaid data	18,987	Atypical antipsychotics: median age 81.0; 72.8% female; 55.3% white, 16.4% black, 4.2% Hispanic, 8.7% Asian, 0.2% other race/ethnicity, 15.2% no valid response Haloperidol: median age 82.0; 72.9% female; 45.2% white, 21.0% black, 4.9% Hispanic, 8.3% Asian, 0.1% other race/ethnicity, 20.6% no valid response

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Confounders adjusted for in study analysis	Results	Funder
Barnett 2007	Age, sex, race, marital status, VA means status, comorbid conditions, previous CVE admission, type of dementia, prescription drug therapy	Risk for new admission for a CVE (Hazard ratio (95% CI)): SGA Quetiapine: 1.0 (Referent) Olanzapine: 0.84 (0.56-2.11) Risperidone: 0.73 (0.41-1.76) Alzheimer-dementia patients: Quetiapine: 1.0 (Referent) Olanzapine: 0.96 (0.39-2.32) Risperidone: 0.79 (0.36-1.71) Vascular-dementia patients: Quetiapine: 1.0 (Referent) Olanzapine: 0.96 (0.39-2.32) Risperidone: 0.79 (0.36-1.71)	Not reported; no conflict of interest was declared
Finkel, 2005 US	Index drug category (risperidone and benzodiazepines as reference groups), age, gender, prior stroke, vascular dementia, severity of illness as assessed by preperiod hospital days, preperiod use of prescribed anticlotting drugs, indicator variables for preperiod comorbidities (hypertension, atherosclerosis, atrial fibrillation, diabetes, hypercholesteremia, carotid artery occlusion), percentage of days study medication was available in the post-index period; and an indicator of the state from which the data were drawn (southern vs nonsouthern states). Race not included due to incomplete data.	95% CI for adjusted odds ratios of an incident cerebrovascular event vs risperidone: (Point estimates reported graphically only) Risperidone (reference) Olanzapine: 0.63-1.73 Quetiapine: 0.23-1.87 Haloperidol: 1.02-3.60	Ortho-McNeil Janssen

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Main outcome	Study design	Study objective
Herrmann, 2004 Canada	CVAEs	Retrospective cohort	To examine the association between atypical antipsychotic use and stroke in the elderly
Layton, 2005 England	CVAEs	Retrospective analysis of 3 observational studies	To compare incidence rates for events reported as cerebrovascular accident (CVA) and transient ischemic attack (TIA) during the first 180 days of treatment in patients prescribed atypical antipsychotics for dementia or other indications.

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Time period covered	Data source/ Inclusion criteria	Sample size	Population characteristics
Herrmann, 2004 Canada	April 1, 1997-March 31, 2002	Administrative health care databases in Ontario, Canada.	11,400 (1,015 typical antipsychotics, 6,964 risperidone, 3,421 olanzapine)	Typical antipsychotics: Mean age 81.1 (SD 7.8) years; 66% female, 33% residing in long-term care facility Risperidone: Mean age 82.9 (SD 7.1) years; 69% female, 43% residing in long-term care facility Typical antipsychotics: Mean age 81.2 (SD 7.5) years; 69% female, 43% residing in long-term care facility
Layton, 2005 England	July 1993-April 1996 (risperidone); December 1996-May 1998 (olanzapine); October 1997-July 1999 (quetiapine)	Prescription event monitoring studies from the Drug Safety Research Unit	18,236 (7684 risperidone, 8826 olanzapine, 1726 quetiapine)	Risperidone: mean age 80 (53-98), 26.1% male, 30.1% dementia, 26.1% other indication, 34.8% indication unknown. Quetiapine: mean age 80 (70-92), 30.0% male, 33.3% dementia, 33.3% other indication, 33.3% indication unknown. Olanzapine: mean age 73 (64-87), 66.7% male, 0% dementia, 80.0% other indication, 20.0% indication unknown.

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Confounders adjusted for in study analysis	Results	Funder
Herrmann, 2004 Canada	Hospitalizations, procedures, and drug utilization hypothesized to be associated with the risk of stroke, demographic characteristics, and number of prescription drugs dispensed in the year before the index date.	Adjusted relative risk (95% CI) of stroke vs typical antipsychotic users: olanzapine: 1.1 (0.5, 2.3) risperidone: 1.4 (0.7, 2.8)	No pharmaceutical industry support received for this study
Layton, 2005 England	Age, sex, indication (dementia or other)	Adjusted relative risk of CVA combined with TIA: olanzapine (reference cohort): 1.0 risperidone: 1.18 (0.47, 2.94) quetiapine: 2.07 (0.56, 7.65) risperidone vs quetiapine: Overall: 1.07 (0.34, 3.30) Dementia: 2.14 (0.45, 10.07) Other indication: 0.42 (0.09, 2.10)	Independent charity, receives donations from pharmaceutical companies. One author received lecture fees from Eli Lilly and Pfizer and support from Pfizer to attend scientific meetings.

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Main outcome	Study design	Study objective
Liperoti, 2005a US	CVAEs	Case-control	To estimate the effect of atypical and conventional antipsychotics on the risk of cerebrovascular events among elderly nursing home patients with dementia
Percudani, 2005 Italy	CVAEs	Retrospective cohort	To investigate the relationship between exposure to second-generation antipsychotics and occurrence of cerebrovascular accidents in the elderly

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Time period covered	Data source/ Inclusion criteria	Sample size	Population characteristics
Liperoti, 2005a US	June 30, 1998-December 27, 1999	Systematic Assessment of Geriatric drug use via Epidemiology (SAGE) database, which contains data from the Minimum Data Set (MDS), with information from Medicare/Medicaid-certified nursing home residents.	1130 cases, 3658 controls	Cases: 11.4% age 74 or younger, 36.1% 75-84, 52.5% 85 or older; 70.5% female; 86.2% white, 11.7% black, 2.1% other race/ethnicity; 23.8% Alzheimer's dementia, 82.9% other dementia Controls: 10.9% age 74 or younger, 39.0% 75-84, 50.1% 85 or older; 71.1% female; 83.2% white, 14.4% black, 2.3% other race/ethnicity; 30.0% Alzheimer's dementia, 79.5% other dementia
Percudani, 2005 Italy	2001	Regional database of hospital admissions and regional database of prescriptions in one region in Italy (Lombardy)	35,604	39.4% age 65-75, 38.7% 76-85, 22.0% over 85

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Confounders adjusted for in study analysis	Results	Funder
Liperoti, 2005a US	Age, sex, race/ethnicity, BMI, indicators of functional, cognitive, and behavioral status, comorbid conditions (hypertension, cardiac ischemic disease, heart failure, cardiac arrhythmias, other cardiac diseases, history of cerebrovascular events, peripheral vascular disease, history of deep vein thrombosis, diabetes mellitus, Alzheimer's disease, other dementias, depression, anxiety disorder, bipolar disorder), and concurrent drug use.	Adjusted OR (95% CI) of being hospitalized with stroke or TIA Risperidone vs no use: 0.87 (0.67, 1.12) Olanzapine vs no use: 1.32 (0.83, 2.11) Other atypical antipsychotic (clozapine and quetiapine) versus no use: 1.57 (0.65, 3.82) Conventional antipsychotic vs no use: 1.24 (0.95, 1.63) Adjusted OR based on history of cerebrovascular events: CVEs history and risperidone use: 1.49 (0.93, 2.38) CVEs history and olanzapine use: 3.71 (1.55, 8.84) CVEs history and other atypical antipsychotic use: 4.63 (1.35, 32.63) CVEs history and conventional antipsychotic use: 1.23 (0.68, 2.23) No CVEs history and risperidone use: 0.83 (0.62, 1.12) No CVEs history and olanzapine use: 1.04 (0.60, 1.80) No CVEs history and other atypical antipsychotic use: 1.02 (0.29, 2.99) No CVEs history and conventional antipsychotic use: 1.36 (1.01, 1.83) CVEs and no use: 1.50 (1.22, 1.84) No CVEs and no use (reference): 1.00	National Institute on Aging, National Institutes of Health
Percudani, 2005 Italy	Age, sex, number of antipsychotic prescriptions, and concomitant prescription of other drugs.	Adjusted OR (95% CI) for risk of cerebrovascular accidents Atypical antipsychotics vs conventional antipsychotics: 1.42 (1.24, 1.64) Clozapine vs haloperidol: 1.44 (0.88, 2.36) Olanzapine vs haloperidol: 1.26 (0.92, 1.72) Risperidone vs haloperidol: 1.43 (1.12, 1.93) Quetiapine vs haloperidol: 1.39 (0.95, 2.05)	Not reported

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Main outcome	Study design	Study objective
Trifiro, 2007 The Netherlands	Mortality, all-cause	Nested case-control	To estimate the association between use of typical and atypical antipsychotics and all-cause mortality in a population of outpatients with dementia
Wang, 2005 US	Mortality, all-cause	Retrospective cohort	To define the risk of death in the short term among elderly patients who were beginning therapy with conventional antipsychotic medications, as compared with the risk among those beginning treatment with atypical antipsychotic agents

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Time period covered	Data source/ Inclusion criteria	Sample size	Population characteristics
Trifiro, 2007 The Netherlands	1996-2004	Integrated Primary Care Information database, a longitudinal general practice database containing data from electronic medical records from 150 GPs in the Netherlands	2385	Patients 65 years or older, with dementia. 32.4% Alzheimer's disease, 13.4% vascular dementia, 54.2% mixed or unspecified dementia. 28.5% received prescriptions for typical antipsychotics; 3.3% for atypical antipsychotics; 2.6% had received both types of drugs.
Wang, 2005 US	January 1, 1994-December 31, 2003	Pennsylvania state prescription-benefits program database; Pennsylvania Medicare	22,890 (39.9% conventional antipsychotics, 60.1% atypical antipsychotics)	Conventional antipsychotics: mean age 83.2, 77.6% female, 92.8% white, 40.8% dementia, 12.2% delirium, 22.2% mood disorders, 21.3% psychotic disorders, 5.9% other psychiatric disorders Atypical antipsychotics: mean age 83.5, 83.0% female, 94.7% white, 52.5% dementia, 16.1% delirium, 36.3% mood disorders, 24.7% psychotic disorders, 8.3% other psychiatric disorders

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Confounders adjusted for in study analysis	Results	Funder
Trifiro, 2007 The Netherlands	Heart failure, COPD, Parkinsonism, home-bound lifestyle, benzodiazepines and antibiotics	Crude mortality rates (per 100 person years) Current use of atypical antipsychotics: 30.1 (18.2-47.1) Current use of typical antipsychotics: 25.2 (21.0-29.8) Overlapping use of atypicals and typicals: 16.5 (3.3-53.0) Adjusted OR for risk of death, current use: Atypical antipsychotics: 2.2 (1.2-3.9) Olanzapine: 6.7 (1.4-32.1) Risperidone: 1.7 (0.9-3.4) Clozapine: 1.8 (0.3-11.2) Quetiapine: no data Typical antipsychotics: 1.7 (1.3-2.2) For both typical and atypical antipsychotics, there was an effect of dose on the association with death; for atypical antipsychotics, risk of death also increased with duration of use.	Not reported; no conflict of interest was declared
Wang, 2005 US	Calendar year, age, sex, race, presence of cardiac arrhythmias, cerebrovascular disease, heart failure, diabetes, MI, other ischemic heart disease, other cardiovascular disorders, cancer HIV infection, dementia, delirium, mood disorders, psychotic disorders, other psychiatric disorders, and the use or nonuse of other psychiatric medications, total number of medications used, hospitalizations, and nursing home stays.	Relative risk of death within 80 days after beginning therapy with conventional antipsychotics as compared with atypical antipsychotics (Hazard ratio, 95% CI): Unadjusted: 1.51 (1.43-1.59) Adjusted analyses: Use of any conventional antipsychotic: 1.37 (1.27-1.49) Low dose (<median): 1.14 (1.04-1.26) High dose (>median): 1.73 (1.57-1.90) With dementia: 1.29 (1.15-1.45) Without dementia: 1.45 (1.30-1.63) In a nursing home: 1.26 (1.08-1.47) Not in a nursing home: 1.42 (1.29-1.56)	NIH, AHRQ

Evidence Table 18. Quality assessment of observational studies in patients with behavioral and psychological symptoms of dementia

	Internal validity			
Author, Year	**Non biased selection**	**Loss to follow-up specified? If yes, low overall loss to follow-up?**	**Outcomes prespecified and defined?**	**Ascertainment techniques adequately described?**
Barnett 2007	Unclear; 6% excluded who had encounters for both Alzheimer- and vascular-type dementia; 1094/15123 (7%) excluded who did not survive until start of observation period; baseline characteristics for individual atypical antipsychotic groups NR	None	Yes	Partly; who ascertained NR
Finkel, 2005	Unclear - number eligible NR, only number included in analysis (n=18,987)	None - patients had to have 3 months from first date of service to be included	Yes	Yes
Hien, 2005	Unclear - 46% participation rate	NR	Yes	Yes

Evidence Table 18. Quality assessment of observational studies in patients with behavioral and psychological symptoms of dementia

Author, Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders	Adequate duration of follow-up	Overall quality rating
Barnett 2007	Yes	Yes	Yes	Fair
Finkel, 2005	Yes	Yes	3 months - defined by duration of RCTs reporting CVEs	Good
Hien, 2005	Unclear - medical records review; no assessment of accuracy	No control for dosage or duration of use	1 month	Fair-Poor

Evidence Table 18. Quality assessment of observational studies in patients with behavioral and psychological symptoms of dementia

	External validity			
Author, Year	**Was description of population adequate?**	**Sample size**	**Exclusion criteria**	**Funder**
Barnett 2007	Yes	14,029	At least 1 encounter for both Alzheimer- and vascular-type dementia; antipsychotic prescription in first 6 months of fiscal year 2002; use of clozapine and injectable antipsychotics; not surviving until start of observation period	Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service, grant from Eli Lilly and Company
Finkel, 2005	Yes	18,987	Use of > one class of study medication in 6 months before or 3 months after initial use of study medication	Ortho-McNeil Janssen
Hien, 2005	No - age ≥ 65 was only eligibility criteria specified; information about presence of the condition of dementia was NR; information about when subjects commenced AAP's also NR	2005	Bed-bound; bilateral lower limb amputation; non-English speaking	National Health and Medical Research Council of Australia

Evidence Table 18. Quality assessment of observational studies in patients with behavioral and psychological symptoms of dementia

	Internal validity			
Author, Year	**Non biased selection**	**Loss to follow-up specified? If yes, low overall loss to follow-up?**	**Outcomes prespecified and defined?**	**Ascertainment techniques adequately described?**
Layton, 2005	Yes	Yes, 31-42% non-response rate	Yes	Yes
Liperoti 2009	Yes	None	Yes	Yes
Raivio, 2007	Yes	NR	Yes	Yes
Trifiro, 2007	Yes	Proportions left practice and impact on resulting duration of follow up NR	Yes	Yes

Evidence Table 18. Quality assessment of observational studies in patients with behavioral and psychological symptoms of dementia

Author, Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders	Adequate duration of follow-up	Overall quality rating
Layton, 2005	Unclear - depended on physician response to questionnaire	Age and sex only	Up to six months exposure, but variable	Fair
Liperoti 2009	Yes	Yes	6 months	Good
Raivio, 2007	Unclear No interrater reliability data collection provided. Medication data only gathered at baseline. No information on medication withdrawals or restarts during the ensuing 2 years	Yes	2 years	Fair
Trifiro, 2007	Yes	Yes	8 years	Good

Evidence Table 18. Quality assessment of observational studies in patients with behavioral and psychological symptoms of dementia

	External validity			
Author, Year	**Was description of population adequate?**	**Sample size**	**Exclusion criteria**	**Funder**
Layton, 2005	No - Demographic characteristics for dementia subgroup NR, only for total cohort	Dementia cohort N=364	NR	DRSU funded by unconditional donations from pharmaceutical companies, included manufacturers of some of the products in this study; last author received lecture fees from Lilly and Pfizer and support from Pfizer to attend scientific meetings
Liperoti 2009	Yes	9,729	Concomitant diagnosis of schizophrenia; use of multiple antipsychotics	National Institute on Aging, National Institutes of Health
Raivio, 2007	Yes	Dementias cohort N = 254	Coma, age under 70 years	Societas Gerontologica Fennica, the Finnish Geriatric Association, the Uulo Arhio Foundation, and the Medical Society of Kyminlaakso, Duodecim, Finland
Trifiro, 2007	Yes	N=2385	NR	NR

Evidence Table 19. Systematic reviews of atypical antipsychotics in youths

Author Year	Aims	Literature search dates	Population included	Drugs included	Study designs included
Canitano, 2008	To review the use of risperidone in children and adolescents with autistic spectrum disorders, particularly regarding the treatment of associated behavioral disorders	Through February 2007	Autism spectrum disorders	Risperidone only	Randomized, placebo controlled trials, observational or retrospective studies and case reports.
Dinca, 2005	To report a systematic review of the randomized or quasi-randomized controlled trials concerning the effectiveness of atypical antipsychotics and SSRIs in the treatment of behavioral problems associated with pervasive developmental disorders.	1966-2004	Diagnosed with a pervasive developmental disorder, excluding Rett's disorder and Childhood Disintegrative Disorder. Diagnosis must have been made using established diagnostic criteria (DSM-III-R, DSM-IV, DSM-IV-R, ICD-10, and/or using a standardized diagnostic instrument.	Oral atypical antipsychotics (also SSRIs): Trials of risperidone, amisulpride and olanzapine identified	Random or quasi-random trials, control group with placebo or alternative medication
Jensen, 2007	To provide a descriptive review of treatment studies of atypical antipsychotics in pediatric psychiatric disorders	January 1994 through March 2006	Pediatric psychiatric disorders	Quetiapine, risperidone, olanzapine, aripiprazole, clozapine, ziprasidone: Trials of olanzapine and risperidone were identified for disruptive behavior disorders and pervasive developmental disorders.	Double-blind or open label clinical trials of >=8 weeks duration with >=20 patients

Evidence Table 19. Systematic reviews of atypical antipsychotics in youths

Author Year	Additional study eligibility criteria	Main results	Subgroups	Adverse events
Canitano, 2008	Not reported	Qualitative synthesis only. Moderate efficacy and safety of risperidone for treating maladaptive behaviors, including aggression, hyperactivity, self injury and irritability.	Efficacy and tolerabiliy of risperidone in the various types of pervasive developmental disorders, including different degress of severity of core symptoms, are still undetermined.	Weight gain most frequent adverse event, ranging from 1 to 10 kg. Weight gain stabilized over time, was more pronounced in first 2 to 3 months of therapy.
Dinca, 2005	At least one standardized measure such as a behavior checklist used for the intervention and control group	No quantitative synthesis. No information on long-term effectiveness and safety. No data on quality of life. Risperidone (2 studies: McCracken 2002, McDougle 1998) effective in moderate-to-severe behavioral problems in children and adolescents with autistic disorder. Olanzapine (1 study: Malone 2001) at low dosage effective for behavioral problems in children with autism and PDD-NOS.	Effectiveness of risperidone and olanzapine cannot be generalized to children with other forms of PDDs.	Risperidone well tolerated, low risk of EPS. Weight gain in children. Olanzapine well tolerated, with no EPS. Weight gain.
Jensen, 2007	Unpublished data or abstracts not included	No quantitative synthesis. Olanzapine (10.7 mg/day) and risperidone (0.49-1.8 mg/day) demonstrated efficacy in reducing symptoms in children with PDD. Risperidone: Effect size vs placebo in 2 studies, based on change from baseline in Aberrant Behavior Checklist-Irritability subscale=-1.2 (McCracken) and -0.8 (Shea) Olanzapine: 1 observational study (Kemner, before-after study) found improvement in ABC and CGI scores.	No information	Risperidone: most common side effects were mild transient somnolence and weight gain. Caregiver-reported tremor or "abnormal movements" (p=0.06 vs placebo) Olanzapine: EPS that resolved with dose adjustment reported.

Evidence Table 19. Systematic reviews of atypical antipsychotics in youths

Author Year	Quality Assessment
Canitano, 2008	1. Report clear review question, state inclusion and exclusion criteria of primary studies? No 2. Substantial effort to find relevant research? No 3. Adequate assessment of validity of included studies? No 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Fair
Dinca, 2005	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Yese 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Good
Jensen, 2007	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Partially 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Partially 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Fair

Evidence Table 19. Systematic reviews of atypical antipsychotics in youths

Author Year	Aims	Literature search dates	Population included	Drugs included	Study designs included
Jesner, 2007 (Cochrane Review)	To determine the efficacy and safety of risperidone for people with autism spectrum disorder	1966-April 2006	Autism spectrum disorders	Risperidone only	Randomized controlled trials of risperidone vs placebo
Parikh, 2008	To systematically and critically examine the evidence for the pharmacological management of aggression and self-injurious behavior in children with autism spectrum disorders.	Searched from beginning of PubMed; end date of searches not reported	Children and adolescents with autism or autism spectrum disorders	Risperidone, others (no other atypical antipsychotics)	Randomized controlled trials of agent versus placebo or active agent

Evidence Table 19. Systematic reviews of atypical antipsychotics in youths

Author Year	Additional study eligibility criteria	Main results	Subgroups	Adverse events
Jesner, 2007 (Cochrane Review)	Trials had to have at least one standardized outcome measure used for both intervention and control group	Overall conclusion: Risperidone beneficial for some features of autism, but limited data available from studies with small sample sizes. Meta-analysis for ABC, CGI, and weight gain ABC mean score vs placebo (Shea 2004 and RUPP 2002): Irritability subscale: -8.09 (95% CI -12.99, -3.19) Social withdrawal/lethargy: -3.00 (95% CI -5.03, -0.97) Hyperactivity: -8.98 (95% CI -12.01, -5.94) Stereotypy: -1.71 (95% CI -2.97, -0.45) Inappropriate speech: -1.93 (95% CI -3.79, -0.07) CGI (McDougle 1998, RUPP 2002, Shea 2004): Relative risk of improvement vs placebo 4.83 (95% CI 2.21, 10.59); significant heterogeneity	No information	Most frequent AEs were somnolence, URTI, rhinitis, and increased appetite. Meta-analysis of weight gain (RUPP 2002, Shea 2004): Risperidone +1.78 kg (95% CI 1.15, 2.41) Placebo 1.0 kg
Parikh, 2008	The use of at least one primary outcome measure with a standardized assessment of aggression and self-injury.	Qualitative synthesis only. Risperidone decreased aggression and self-injurious behavior in 3 placebo-controlled trials	Not addressed	Weight gain associated with risperidone treatment

Evidence Table 19. Systematic reviews of atypical antipsychotics in youths

Author Year	Quality Assessment
Jesner, 2007 (Cochrane Review)	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Yes 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Good
Parikh, 2008	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Partially 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Fair

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/washout period
Olanzapine vs. haloperidol						
Malone, 2001 US (FAIR)	12	6 weeks	Randomized, open label, pilot study.	Children between ages 5 and 17 with a primary diagnosis of pervasive developmental disorder (DSM-IV criteria); at least moderate impairment on 2 or more of the first 28 items on the Children's Psychiatric Rating Scale at baseline.	Olanzapine starting dose 2.5 mg every other day for patients who weighed 40 kg or less and 2.5 mg per day for those who weighed more than 40 kg. Dosages could be increased in 2.5 mg increments up to 5 mg per week as needed. Maximum dose 20 mg/day. Haloperidol starting dose 0.25 mg/day for patients weighing 40 kg or less and 0.5 mg for those who weighed more than 40 kg. Dosages could be increased as clinically indicated in 0.5 mg increments up to 1 mg per week as needed. Maximum dose 5 mg/day.	1 week drug-free baseline washout period.
Risperidone vs. haloperidol						
Gencer 2008 Turkey	28	12 weeks after initial study	open-label continuation study of the randomized, double-blind, controlled trial Single center	Children and adolescents with a primary diagnosis of AD according to the DSM-IV criteria	Haloperidol mean 2.7 ± 1.3 mg/day Risperidone mean = 2.5 ± 0.7 mg/day in the risperidone	Followed RCT

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Olanzapine vs. haloperidol					
Malone, 2001 US (FAIR)	No	Mean age 7.8 (SD 2.1) years; range 4.8-11.8 years. 67% male 58% white, 25% African American, 17% Hispanic	11/12 (92%) autistic disorder, 1/12 (8%) pervasive developmental disorder, not otherwise specified. 8% normal cognitive functioning, 8% mild mental retardation, 42% moderate mental retardation, 42% severe mental retardation.	# screened not reported/ 13 eligible/ 12 enrolled (1 withdrew consent)	No withdrawals, losses to followup, 12 analyzed.
Risperidone vs. haloperidol					
Gencer 2008 Turkey	antianalgesics, antipyretics, decongestants and antibiotics administered by other doctors throughout the study as well as Anticholinergic agents for EPS	Mean age 10.5 % male 79 Ethnicity NR	None of interest	NR/NR/28	1/0/27

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Outcome measures	Method of outcome assessment and timing of assessment	Results
Olanzapine vs. haloperidol			
Malone, 2001 US (FAIR)	Primary outcome: CGI Secondary outcome: Children's Psychiatric Rating Scale (CPRS)	Principal investigator and one other trained rater performed all ratings; assessments at baseline and end of study.	CGI Improvement from baseline olanzapine: 1/6 (16.7%) very much improved 4/6 (66.7%) much improved 1/6 (16.7% minimally improved haloperidol: 1/6 (16.7%) very much improved 2/6 (33.3%) much improved 3/6 (50% minimally improved (p=0.494) Mean change from baseline (olanzapine vs haloperidol) CGI (Severity): -1.08 vs -0.42 CPRS (Autism): -0.84 vs -0.53 CPRS (Anger/Uncooperative): -1.27 vs 0.15 CPRS (Hyperactivity): -1.1 vs 0.36 CPRS (Speech Deviance): 0.4 vs -0.25
Risperidone vs. haloperidol			
Gencer 2008 Turkey	Clinical Global Impression Scales-Improvement (CGII), Ritvo-Freeman Real Life Rating Scale (RFRLRS), Aberrant Behavior Checklist (ABC) and Turgay DSM-IV Pervasive Developmental Disorder Rating Scale (TPDDRS)	At week 12 of the double-blind study and were repeated at weeks 16, 20 and 24.	Risperidone vs. haloperidol baseline/endpoint RF-RLRS (Sensory-motor) 0.90 ± 0.52/ 0.44 ± 0.42 vs. 0.69 ± 0.47 / 0.57 ± 0.48 P = 0.1828 RF-RLRS (Social) 0.62 ± 0.50 / 0.69 ± 0.42 vs. 0.50 ± 0.41 / 0.68 ± 0.59 P = 0.6141 RF-RLRS (Affect) 1.09 ± 0.41 / 1.27 ± 0.37 vs.. 1.05 ± 0.61 / 1.36 ± 0.68 P = 0.6141 RF-RLRS (Sensory) 0.98 ± 0.46 / 0.82 ± 0.35 vs. 0.86 ± 0.44 / 0.81 ± 0.59 P = 0.7551 RF-RLRS (Language) 0.52 ± 0.37 / 0.44 ± 0.33 vs. 0.15 ± 0.44 / 0.32 ± 0.51 P = 0.0414 ABC (Total) 85.6 ± 27.3 / 52.0 ± 14.9 vs. 67.1 ± 25.1 / 58.1 ± 32.2 P = 0.0746 TPDDRS 91.5 ± 20.1 / 67.2 ± 17.0 vs. 77.6 ± 23.1 / 66.2 ± 26.4 P = 0.0594 CGI degree of improvement P = 0.0186 (no other numbers reported for this outcome

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Method of adverse effects assessment	Withdrawals/ withdrawals due to AEs	Adverse events
Olanzapine vs. haloperidol			
Malone, 2001 US (FAIR)	Weight, blood pressure, and pulse at baseline and each visit. Height recorded at baseline. Adverse effects monitored at each visit with the Dosage Record and Treatment Emergent Symptom Scale (DOTES), the Treatment Emergent Symptoms Scale-Write IN (TESS), AIMS, and the Neurologic Rating Scale (NRS). At baseline and end of treatment, complete blood count with differential, liver functions, and EKG.	None	Mean weight gain at 12 weeks: olanzapine: 4.08 kg (SD 1.59, range 2.67 to 7.14) haloperidol: 1.45 kg (SD 2.22, range -2.49 to 3.97) (p=0.04) All 6 patients in olanzapine group vs 2 of 6 in haloperidol group gained more than 2.27 kg (5 lbs) No significant differences between groups on incidence of side effects. NRS: One haloperidol patient had transient mild rigidity, no olanzapine patient had extrapyramidal symptoms as rated by this measure. AIMS: No patients in either treatment group had dyskinesia as rated by this measure. No clinically significant changes in any of the laboratory studies or EKGs. Medication treatment was not associated with a prolongation of the QTc interval.
Risperidone vs. haloperidol			
Gencer 2008 Turkey	Extrapyramidal Symptoms Rating Scale (ESRS) and UKU Side-Effect Rating Scale	1 withdrawal 0 due to AEs	Weight gain was observed more frequently in the haloperidol group. P = 0.0414 Risperidone vs. haloperidol % URTI 53.1 vs. 53.85 enuresis nocturna 23.1 vs. 20

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/washout period
Miral 2008 Turkey	30	12 week total ; 2 weeks screening and 10 weeks RCT	DB RCT Single center	Autistic Disorder; be 8–18 years; have his or her parents' informed consent, and agree to be followed-up.	Haloperidol mean = 2.6 ± 1.3 mg/day Risperidone mean = 2.6 ± 0.8 mg/day	2 week screening

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Miral 2008 Turkey	antianalgesics, antipyretics, decongestants and antibiotics administered by other doctors throughout the study as well as Anticholinergic agents for EPS	Mean age 10.5 % male 80 Ethnicity NR	None of interest	NR/NR/32	2/2 LTF/30

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Outcome measures	Method of outcome assessment and timing of assessment	Results
Miral 2008 Turkey	Ritvo–Freeman Real Life Rating Scale (RF-RLRS), CGI Severity and Improvement	Assessed at baseline and 2, 4, 8, and 12.	Risperidone vs. haloperidol Ritvo–Freeman Real Life Rating Scale Social Baseline 0.62 ± 0.50 vs. 0.50 ± 0.41 Endpoint)0.11 ± 0.38 vs. 0.02 ± 0.57 Sensory motor Baseline 0.90 ± 0.52 vs. 0.69 ± 0.47 End-point 0.36 ± 0.34 vs. 0.50 ± 0.44 Affect Baseline 1.09 ± 0.41 vs. 1.05 ± 0.61 End-point 0.54 ± 0.34 vs. 0.64 ± 0.48 Sensory Baseline 0.98 ± 0.46 vs. 0.86 ± 0.44 End-point 0.51 ± 0.25 vs. 0.58 ± 0.49 Language Baseline 0.52 ± 0.37 vs. 0.15 ± 0.44 End-point 0.04 ± 0.25 vs. 0.05 ± 0.5 Aberrant Behavior Checklist Baseline 85.6 ± 27.3 vs. 67.1 ± 25.1 End-point 36.8 ± 13.8 vs. 45.8 ± 20.2 CGI-I scores, Markedly improved 15.4% vs. 0 Moderately improved,69.2% vs. 60% Slightly improved 15.4% vs. 33.3% No change 0 vs. 6.7%

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Method of adverse effects assessment	Withdrawals/ withdrawals due to AEs	Adverse events
Miral 2008 Turkey	Turgay DSM-IV PDD Rating Scale ABC, ESRS, The UKU Side-effect rating Scale.	2 withdrawals 0 due to AEs	Risperidone vs. haloperidol Enuresis nocturna 23.1% vs. 20% URTI 53.8% vs. 53.3% Chouinard Extrapyramidal Symptoms Rating Scale Section I Baseline 0.23 ± 0.60 vs. 0.33 ± 0.82 End-point 0.15 ± 0.38 vs. 1.27 ± 1.75 Parkinsonism Baseline 0.00 vs. 0.00 End-point 0.00 vs. 0.00 Dystonia Baseline 0.00 vs. 1 0.00 End-point 0.00 vs. 0.00 Dyskinesia Baseline 0.00 vs. 0.3173 0.40 ± 1.55 End-point 0.08 ± 0.28 vs. 0.13 ± 0.30 Turgay DSM-IV Scores Baseline 91.5 ± 20.1 vs. 0.0019 77.6 ± 23.1 End-point 53.5 ± 9.6 vs. 59.6 ± 21.3

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/washout period
Aripiprazole						
Marcus 2009 United States	218	8 weeks	RCT, DB Multicenter (37)	Inclusion: Aged 6 to 17 years weighing ≥15 kg; met DSM-IV-TR criteria for autistic disorder; with behaviors such as irritability, agitation, self-injurious behavior, or a combination of these; and CGI-S ≥4 and ABC-Irritability (ABC-I) subscale ≥18 at screening and baseline. Exclusions: bipolar disorder, psychosis, schizophrenia or major depression, fragile X, or another autistic spectrum disorder including PDD not otherwise specified, Asperger's, Rett, or childhood disintegrative disorder; hx of neuroleptic malignant syndrome, stroke, or head trauma; suicide risk; seizure in past year; unstable medical condition or abnormal lab, clinical, or ECG finding.	4 groups: Placebo (N=52); Aripiprazole 5 mg/day (N=53); 10 mg/day (N=59); 15 mg/day (N=54) Subjects randomized to aripiprazole started at 2 mg/day for the first week, increased to 5 mg/day the 2nd week, increasing weekly by 5 mg for higher dose groups. Subjects unable to tolerate assigned dose were discontinued from study. 8 weeks	Screening/washout phase up to 42 days

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Aripiprazole					
Marcus 2009 United States	Antianxiety (benzodiazepines); sleep aids (diphenhydramine and non-benzodiazepine hypnotics); diphenhydramine up to 50 mg/day for serious behavior problems; psychotropic meds for acute treatment; anticholinergics or propranolol for EPS	Mean age 9.7 years 76.1% aged 6-12 89.4% male white 71.1% black 22.9% Asian 2.8% other 3.2%	Mean ABC-I at baseline 28.4 30% CGI-S=4, moderately ill 40% CGI-S=5, markedly ill 30% CGI-S=7, severely ill	368/218/218	40/5/213

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Outcome measures	Method of outcome assessment and timing of assessment	Results
Aripiprazole			
Marcus 2009 United States	Primary: Mean change from baseline to endpoint in caregiver-rated ABC-Irritability subscale score. Secondary: CGI-I score at endpoint; change in other ABC subscales and Children's Y-BOCS; response rate (≥25% reduction in ABC-I and a CGI-I=1 or 2 at endpoint); Pediatric Quality of Life Inventory (PedsQL); CGI-S; Caregiver Strain Questionnaire (CGSQ).	Assessed at baseline and weeks 1, 2, 3, 4, 5, 6, and 8.	Placebo vs. Aripiprazole 5 / 10 / 15 mg/day: Completed study: 73.1 vs. 83 / 83.1 / 87% ABC-I subscale score, mean change from baseline to week 8: -8.4 vs. -12.4 (P=0.032) / -13.2 (P=0.008) / -14.4 (P=0.001) Response rate at week 8, %: 34.7 vs. 55.8 (P=0.034) / 49.2 (P=ns) / 52.8 (P=ns) CGI-I 3.3 vs. 2.6 (P=0.003) / 2.5 (P<0.001) / 2.5 (P<0.001) CGI-S mean ±SE change at week 8: -0.6 ±0.2 vs. -0.9 ±0.1 / -1.0 ±0.1 / -1.1 ±0.2 Treatment difference (95% CI): (ref.) vs. -0.3 (-0.7 to 0.1) / -0.4 (-0.8 to -0.0) / -0.6 (-1.0 to -0.2) Aripiprazole 15mg/day vs. placebo, mean treatment difference: PedsQL: 8.2 (95%CI 1.2 to 15.2). CGSQ: -1.1 (95%CI -1.9 to -0.3)

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Method of adverse effects assessment	Withdrawals/ withdrawals due to AEs	Adverse events
Aripiprazole			
Marcus 2009 United States	Reports of adverse events; vital signs; ECG findings; and weight and lab assessments, including prolactin levels. EPS assessed using SAS; BARS; AIMS	40 withdrawals 21 due to AE	Placebo vs. Aripiprazole 5 / 10 / 15 mg/day, % of group: Sedation 5.9 vs. 17.3 / 28.8 / 24.1 Tremor 0 vs. 7.7 / 11.9 / 11.1 Somnolence 3.9 vs. 7.7 / 8.5 / 9.3 Drooling 0 vs. 3.8 / 13.6 / 9.3 Headache 3.9 vs. 5.8 / 8.5 / 9.3 Extrapyramidal disorder 0 vs. 3.8 / 6.8 / 11.1 Lethargy 0 vs. 7.7 / 5.1 / 5.6 Hypersomnia 0 vs. 5.8 / 0 / 3.7 Vomiting 7.8 vs. 9.6 / 20.3 / 9.3 Salivary hypersecretion 2.0 vs. 1.9 / 6.8 / 11.1 Nausea 2.0 vs. 1.9 / 5.1 / 7.4 Abdominal pain upper 2.0 vs. 3.8 / 1.7 / 7.4 Fatigue 0 vs. 3.8 / 22.0 / 18.5 Pyrexia 0 vs. 5.8 / 11.9 / 9.3 Increased appetite 3.9 vs. 19.2 / 5.1 / 13.0 Weight increased 2.0 vs. 7.7 / 1.7 / 3.7 Gained ≥7% body weight: 8.2 vs. 32.7 / 15.3 / 30.2 EPS: 11.8 vs. 23.1 / 22.0 / 22.2 Presyncope in 1 subject on aripiprazole 5 mg/day, day 17. HDL <30 mg/dL occurred in 3 subjects on aripiprazole, but 2 had abnormalities at baseline. Elevated prolactin in 0% on aripiprazole and 4.4% on placebo.

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/washout period
Owen 2009 United States	98	8 weeks	RCT, DB Multicenter (20)	Inclusion: Aged 6 to 17 years weighing ≥15 kg; met DSM-IV-TR criteria for autistic disorder; with behaviors such as irritability, agitation, self-injurious behavior, or a combination of these; and CGI-S ≥4 and ABC-Irritability (ABC-I) subscale ≥18 at screening and baseline. Exclusions: bipolar disorder, psychosis, schizophrenia or major depression, fragile X, or another autistic spectrum disorder including PDD not otherwise specified, Asperger's, Rett, or childhood disintegrative disorder; hx of neuroleptic malignant syndrome, stroke, or head trauma; suicide risk; seizure in past year; unstable medical condition or abnormal lab, clinical, or ECG finding.	Flexibly dosed aripiprazole (maximum 15 mg/day) starting at 2 mg/day, with target dose of 5, 10, or 15 mg/day. Placebo 8 weeks	Screening/washout phase up to 6 weeks

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Owen 2009 United States	Lorazepam or alprazolam for anxiety; sleep aids (diphenhydramine, melatonin, or nonbenzodiazepine hypnotics); diphenhydramine up to 50 mg/day for serious behavior problems; benztropine or propranolol for EPS.	Mean age 9.2 years 87.8% male White 74.5% Black 18.4% Asian 2.0% Other 5.1%	ABC irritability subscale score at baseline, mean 29.9 Mean weight, kg 42.2	164 enrolled in screening phase / 98 eligible for randomization / 98 enrolled in DB phase	23/1/95

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Outcome measures	Method of outcome assessment and timing of assessment	Results
Owen 2009 United States	Primary: Mean change from baseline to endpoint in caregiver-rated ABC-Irritability subscale score. Secondary: CGI-I score at endpoint; change in other ABC subscales and Children's Y-BOCS; response rate (≥25% reduction in ABC-I and a CGI-I=1 or 2 at endpoint); Pediatric Quality of Life Inventory (PedsQL); CGI-S; Caregiver Strain Questionnaire (CGSQ).	Assessed at baseline and weeks 1, 2, 3, 4, 5, 6, and 8.	Aripiprazole (N=46) vs. placebo (N=49): ABC-irritability subscale score mean change at week 8: -12.9 vs. -5.0 Least-squares mean treatment difference -7.9, 95%CI -11.7 to -4.1; P<0.001. CGI-I at week 8: 2.2 vs. 3.6; treatment difference -1.4; 95%CI -1.9 to -1.0; P<0.001 CGI-S mean change: -1.2 vs. -0.4; treatment difference -0.8; 95%CI -1.2 to -0.4); P<0.001 CY-BOCS (compulsions only): -3.8 vs. -0.8; treatment difference -3.0; 95%CI -4.3 to -1.6; p<0.001 Response rate at week 2: 30.4% vs. 4.1%; P<0.001 Response rate at week 8: 52.2% vs. 14.3%; P<0.001 PedsQL combined scales total score, treatment difference 11.4; 95%CI 6.1 to 16.8 CGSQ global score, treatment difference -1.9; 95% CI -2.7 to -1.2

Evidence Table 20. Active-control trials of atypical antipsychotics in youths

Author, year Country Trial name (Quality score)	Method of adverse effects assessment	Withdrawals/ withdrawals due to AEs	Adverse events
Owen 2009 United States	Reports of adverse events; vital signs; ECG findings; and weight and lab assessments, including prolactin levels. EPS assessed using SAS; BARS; AIMS	23 withdrawals 8 due to AE	Placebo (N=50) vs. Aripiprazole (N=47), % of group: Headache 16 vs 6.4 Somnolence 4 vs 17 Sedation 2 vs 10.6 Drooling 0 vs 8.5 Tremor 0 vs 8.5 Diarrhea 10 vs 8.5 Vomiting 4 vs 14.9 Insomnia 8 vs 6.4 Aggression 8 vs 2.1 Fatigue 4 vs 21.3 Pyrexia 2 vs 8.5 Increased appetite 10 vs 14.9 Weight gain ≥ 7%: 6.1 vs. 28.9; P<0.01 Any EPS event 8 vs 14.9 Tremor 0 vs 8.5 Extrapyramidal disorder 0 vs 2.1 Muscle rigidity 0 vs 2.1 Hypokinesia 0 vs 2.1 Prolactin level change: 1.6 vs -6.3 ng/mL; P<0.001 Prolactin elevation: 6.8% vs. 2.4%

Evidence Table 21. Quality assessment of trials in youths

	Internal validity						
Author, year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Studies in children with autism							
Active-control trials							
Gencer 2008	NR	NR	Yes	Yes	NR (described as double-blind)	NR (described as double-blind)	NR (described as double-blind)
Malone et al, 2001 US	Yes	Not reported	Yes	Yes	No	No	No
Miral 2008	NR	NR	Yes, except for height	Yes	NR (described as double-blind)	NR (described as double-blind)	NR (described as double-blind)
Placebo-controlled trials							
Hollander, 2006 US double blind placebo-controlled Olanzapine Poor	Method not reported	Method not reported	Yes	Yes	NR	NR	Yes
Luby, 2006 US Randomized, placebo-controlled Risperidone Fair	Yes	Yes	Yes on most measures; tx group greater severity of autism symptoms at baseline, poorer language skills, and poorer motor skill development.	Yes	Yes	No	Yes

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Studies in children with autism					
Active-control trials					
Gencer 2008	Yes, No, No, No	No/No	Yes	No	Fair
Malone et al, 2001 US	Not reported	No	Yes	No	Fair
Miral 2008	Yes, No, No, No	No/No	No	No	Fair
Placebo-controlled trials					
Hollander, 2006 US double blind placebo-controlled Olanzapine Poor	Attrition, Yes Cross over, NA Adherence, No Contamination, No	6 tx; 4 completed 5 placebo; 4 completed	No	No	Poor
Luby, 2006 US Randomized, placebo-controlled Risperidone Fair	Attrition, Yes Cross over, NA Adherence, No Contamination, No	No/No 1 subject of 24 total	No; may not be applicable since only one did not complete?	No	Fair

Evidence Table 21. Quality assessment of trials in youths

	External validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**
Studies in children with autism			
Active-control trials			
Gencer 2008	NR/NR/28	Had epilepsy, had a concomitant neuropsychiatric illness, demonstrated a psychotic disorder or symptoms, had other pervasive developmental disorders.	No/No
Malone et al, 2001 US	Number screened, eligible not reported/12 enrolled	Major medical problems such as cardiac, liver, endocrine, or renal diseases, seizure disorder or gross neurological deficit, treatment with concomitant psychotropic medication, or a history of previous treatment with haloperidol or olanzapine.	1 week drug-free baseline washout period.
Miral 2008	NR/NR/32	Had epilepsy, had a concomitant neuropsychiatric illness, demonstrated a psychotic disorder or symptoms, had other pervasive developmental disorders.	No/No
Placebo-controlled trials			
Hollander, 2006 US double blind placebo-controlled Olanzapine Poor	Number screened or eligible not reported// 11 enrolled	Subjects who were responding well to prior pharmacological treatment were excluded. Exclusion criteria also included psychotic disorders and a history of any clinically significant medical illness (with the exception of a stable seizure disorder). Patients were required to be free of psychotropic medications for at least 4 weeks prior to starting the study drug with the exception of stable dose (at least 3 months) of anticonvulsants for seizures or clonidine or chloral hydrate given only at bedtime for sleep. None of the patients was taking any concomitant medications during the study.	Run-in, Yes Washout, Yes
Luby, 2006 US Randomized, placebo-controlled Risperidone Fair	Number screened or eligible not reported/ 24 enrolled/23 completed	Excluded if 1) other known significant central nervous system (CNS) disorders; and (2) significant medical problems or other psychiatric disorders requiring pharmacotherapy, or 3) other neurological and medical illness.	Run-in, Yes Washout, Yes

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding	Comments
Studies in children with autism				
Active-control trials				
Gencer 2008	No	No	Janssen and Cilag Drug Company	
Malone et al, 2001 US	Yes	Yes	Supported in part by a grant from Lilly Research Laboratories (Investigator-Initiated Study).	
Miral 2008	No	No	Janssen and Cilag Drug Company	
Placebo-controlled trials				
Hollander, 2006 US double blind placebo-controlled Olanzapine Poor	No	Yes	This study was supported by an investigator-initiated research grant from Lilly Research Laboratories. Olanzapine and matching placebo were supplied by Lilly Research Laboratories. We acknowledge Charles Cartwright, M.D., and Sallie Jo Hadley, M.D.	Small study, No ITT, No details on randomization
Luby, 2006 US Randomized, placebo-controlled Risperidone Fair	NR	Yes	Funded by Janssen Pharmaceutica	small study

Evidence Table 21. Quality assessment of trials in youths

	Internal validity						
Author, year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Nagaraj, 2006 India double blind placebo-controlled Risperidone Fair	Yes	Yes	Yes	Yes	Yes	NR	Yes
Marcus 2009	Method not reported	Method not reported	No Placebo group heavier	Yes	NR (described as double-blind)	NR (described as double-blind)	NR (described as double-blind)
McCracken et al, 2002 Arnold et al, 2003 Research Units on Pediatric Psychopharmacology Autism Network RUPP	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes
Owen 2009	Yes	Yes	No Drug group older and heavier	Yes	Yes	NR (described as double-blind)	NR (described as double-blind)
Shea et al, 2004 Pandina et al, 2004 (subgroup analysis) Canada	Method not reported	Not reported	Yes	Yes	Yes	Not reported	Yes

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Nagaraj, 2006 India double blind placebo-controlled Risperidone Fair	Attrition, Yes Cross over, NA Adherence, No Contamination, No	No/No 1 of 20 placebo	No; may not be applicable since only one did not complete?	No	Fair-Good
Marcus 2009	Yes, No, Yes, No	No, no	No 3/218 excluded from efficacy sample	Yes	Fair
McCracken et al, 2002 Arnold et al, 2003 Research Units on Pediatric Psychopharmacology Autism Network RUPP	Attrition yes, others no.	No	Yes	Yes- 4 patients.	Fair
Owen 2009	Yes, No, No, No	No, no	No 2/98 excluded from efficacy sample	Yes	Fair
Shea et al, 2004 Pandina et al, 2004 (subgroup analysis) Canada	Attrition yes, others no.	No	Yes (1 not analyzed)	No	Fair

Evidence Table 21. Quality assessment of trials in youths

	External validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**
Nagaraj, 2006 India double blind placebo-controlled Risperidone Fair	Number screened or eligible not reported/ 40 enrolled/39 completed	Subjects were excluded if one or more of the following were present: (1) severe mental retardation, (2) any significant coexisting disease or illness (neurologic, cardiovascular, respiratory, genetic), or (3) severe malnutrition (weight for age < 60% of National Center for Health Statistics median), the latter because malnutrition itself can cause subtle behavioral changes, especially with regard to social interaction and emotional responses.	Run-in, Yes Washout, Yes
Marcus 2009			
McCracken et al, 2002 Arnold et al, 2003 Research Units on Pediatric Psychopharmacology Autism Network RUPP	270 screened/158 eligible/101 enrolled	Serious medical disorders and other psychiatric disorders requiring medication; receiving a psychotropic drug that was deemed effective for the treatment of aggression, tantrums, or self-injurious behavior.	Ineffective medications gradually withdrawn, drug-free interval of 7 to 28 days, depending on the drug, was required before enrollment.
Owen 2009			
Shea et al, 2004 Pandina et al, 2004 (subgroup analysis) Canada	Number screened, eligible not reported/80 enrolled	Schizophrenia, other psychotic disorders, clinically relevant nonneurologic disease, clinically significant laboratory abnormalities, or a seizure disorder for which they were receiving >1 anticonvulsant or if they had had a seizure in the last 3 months. History of hypersensitivity to neuroleptics, tardive dyskinesia, neuroleptic malignant syndrome, drug or alcohol abuse, or HIV infection. Also excluded subjects who had used risperidone in the last 3 months, had been previously unresponsive or intolerant to risperidone, or were using a prohibited medication.	None reported.

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding	Comments
Nagaraj, 2006 India double blind placebo-controlled Risperidone Fair	No	Yes	Funding provided by Department of Pediatrics and the institute's internal finances. [Sun Pharmaceuticals, Mumbai, India, provision of the drug and placebo in the required format for the study.]	
Marcus 2009				
McCracken et al, 2002 Arnold et al, 2003 Research Units on Pediatric Psychopharmacology Autism Network RUPP	No	Yes	Supported by contracts from the National Institute of Mental Health, General Clinical Research Center grants from the National Institutes of Health, and a grant from the Korczak Foundation. Study medication donated by Janssen Pharmaceutica.	
Owen 2009				A high fair - if all had been included in ITT, rating would be good
Shea et al, 2004 Pandina et al, 2004 (subgroup analysis) Canada	No	Yes	Supported by Janssen-Ortho Inc, Canada, and Johnson & Johnson Pharmaceutical Research and Development.	

Evidence Table 21. Quality assessment of trials in youths

	Internal validity						
Author, year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Studies in children with disruptive behavior disorders							
Placebo-controlled trials							
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US	Method not reported	Not reported	Differences in IQ, but controlled for in analysis	Yes	Yes	Yes	Yes
Armenteros, 2007 US	Yes	Not reported	Yes	Yes	Yes	Yes	Yes
Buitelaar, 2001 Netherlands	Yes	Not reported	Yes	Yes	Yes	Yes	Yes

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Studies in children with disruptive behavior disorders					
Placebo-controlled trials					
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US	Attrition and adherence yes, others no.	Yes- 78% risperidone, 70% placebo.	No- 3 risperidone patients with no efficacy data not included in analysis.	Not reported	Fair
Armenteros, 2007 US	Yes, No, No, No	None	Yes	No	Good
Buitelaar, 2001 Netherlands	Yes	No	Yes (LOCF)	No	Fair

Evidence Table 21. Quality assessment of trials in youths

	External validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**
Studies in children with disruptive behavior disorders			
Placebo-controlled trials			
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US	142 screened/119 eligible/118 enrolled	Diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorder; head injury as a cause of intellectual disability; or a seizure disorder requiring medication. Known hypersensitivity to risperidone or neuroleptics, history of tardive dyskinesia or neuroleptic malignant syndrome, serious or progressive illnesses, presence of HIV, and use of an investigational drug within the previous 30 days; previous treatment with risperidone.	1-week placebo run-in to rule out placebo responders.
Armenteros, 2007 US	NR/NR/25	If they had a substance use disorder, an unstable medical or neurological illness, a history of intolerance or failure to respond to an adequate trial of risperidone (defined as 2 mg/day for at least 4 weeks), or the patients was suicidal or homicidal. Subjects were allowed to continue receiving any psychosocial treatment that was in place before entering the study. However, subjects were not allowed to seek psychosocial interventions during the study.	NR/NR
Buitelaar, 2001 Netherlands	145/48/38	Neurologic, cardiac, pulmonary, or hepatic diseases, primary mood disorders, schizophrenia or other active psychosis, or suicidality, comorbid substance abuse disorder according to DSM-IV; if female, pregnant or used inadequate contraception; major change in treatment strategy (such as transition to another ward) was expected in the near future; or it was not considered feasible to discontinue current psychotropic medication.	No run-in; 2 week washout after double-blind period.

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding	Comments
Studies in children with disruptive behavior disorders				
Placebo-controlled trials				
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US	Yes	Yes	Supported by the Janssen Research Foundation.	
Armenteros, 2007 US	No	Yes	First author has received research support and is on speakers panel of Janssen	
Buitelaar, 2001 Netherlands	NR	Yes	Janssen-Cilag, The Netherlands	

Evidence Table 21. Quality assessment of trials in youths

	Internal validity						
Author, year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Connor 2008	NR	NR	Yes	Yes	NR (described as double-blind)	Yes	Yes
Findling et al, 2000 US	Yes	Yes	Trends: risperidone group older (p=0.006) and weighed more (p=0.12)	Yes	Yes	Yes	Yes

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Connor 2008	Yes, No, No, No	Differential: Yes High: Yes 8/9 (88%) completed in Quetiapine group 3/10 (30%) completed in placebo group (most dropped due to lack of efficacy; N=5)	Yes	2 excluded for "protocol violations"	Fair
Findling et al, 2000 US	Attrition and adherence yes, others no.	Withdrawals- 40% risperidone, 70% placebo	Yes	No	Fair

Evidence Table 21. Quality assessment of trials in youths

	External validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**
Connor 2008	NR/68/20	A co-morbid psychiatric diagnosis of schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified, bipolar disorder, psychotic depression, or bipolar disorder not otherwise specified; alcohol or substance abuse or dependence within 3 months of study entry; significant subaverage IQ as assessed by clinician; current or past history of lenticular abnormality or juvenile cataracts; seizure disorder; concurrent administration of any psychoactive medication; pregnant or lactating females; women of childbearing potential not using a medically accepted means of birth control; any unstable medical disease that in the opinion of the clinician contraindicated study participation.	1 week single-blind placebo/4-week washout period for psychoactive medications
Findling et al, 2000 US	Number screened, eligible not reported/20 enrolled.	Moderate or severe attention deficit/hyperactivity disorder, significant psychiatric comorbidity (including mood disorders), treatment with a psychotropic medication within one week of initiating double-blind therapy, a positive toxicology screen, suicide attempt within the past month, clinically significant general medical condition, organic mental syndromes, pregnant or nursing females, females of childbearing potential who were not using an acceptable method of birth control, and a standard score equivalent to <70 on the Peabody Picture Vocabulary Test-Revised.	None reported.

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding	Comments
Connor 2008	No	Yes	AstraZeneca	
Findling et al, 2000 US	No	Yes	Supported in part by the Janssen Research Foundation, the Stanley Foundation, and NICHD Pediatric Pharmacology Research Unit contract.	

Evidence Table 21. Quality assessment of trials in youths

	Internal validity						
Author, year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Reyes, 2006 International [8 countries, non-US] double blind placebo-controlled Risperidone Fair-Poor	Unclear; the randomization code was generated by the study sponsor, with treatment numbers allocated at each investigative center in chronological order.	Yes	Yes	Yes	NR	NR	Yes
Snyder et al, 2002 Risperidone Conduct Study Group Canada, US, South Africa	Method not reported	Not reported	Yes	Yes	Yes	Yes	Yes

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Reporting of attrition, crossovers, adherence, and contamination?	Loss to follow-up: Differential/high?	Intention-to-treat (ITT) analysis?	Post-randomization exclusions?	Quality rating
Reyes, 2006 International [8 countries, non-US] double blind placebo-controlled Risperidone Fair-Poor	Attrition, Yes Cross over, NR Adherence, NR Contamination, NR	Discontinuation due to adverse effects 1.7% with risperidone, 0.6% with placebo (maintenance phase).	No	Unclear	Fair-Poor
Snyder et al, 2002 Risperidone Conduct Study Group Canada, US, South Africa	Attrition yes, others no.	Yes- 33.3% placebo, 11.3% risperidone withdrew (p=0.006)	No	No	Fair

Evidence Table 21. Quality assessment of trials in youths

	External validity		
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**
Reyes, 2006 International [8 countries, non-US] double blind placebo-controlled Risperidone Fair-Poor	575/527/335 randomized for 6 month double blind phase of study; 162 (48% completed)	Exclusions: moderate or severe intellectual impairment (IQ ≥55) as determined at screening or within the preceding 3 years. Those with other serious medical or psychiatric conditions such as schizophrenia or bipolar disorder were excluded. Concomitant therapy with stable psychostimulant dosing was permitted (i.e., patients must have been receiving a stable dose of psychostimulants for at least 30 days before study entry and that dose must have been maintained by the clinician). Treatment with additional antipsychotics, lithium, anticonvulsants, or antidepressants was not permitted. If no reliable caregiver to provide assessments and ensure medication compliance was available, patient was excluded.	Run-in, Yes Washout, No
Snyder et al, 2002 Risperidone Conduct Study Group Canada, US, South Africa	Number screened not reported/133 eligible/110 enrolled	Diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorder; head injury as a cause of impaired IQ; seizure condition requiring medication; females who were sexually active without a reliable form of birth control; serious or progressive illness or clinically abnormal laboratory values; history of tardive dyskinesia, neuroleptic malignant syndrome, or hypersensitivity to any antipsychotic drug; known presence of HIV; and previous treatment with risperidone.	One week placebo run-in to rule out placebo responders.

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Class naïve patients only?	Control group standard of care?	Funding	Comments
Reyes, 2006 International [8 countries, non-US] double blind placebo-controlled Risperidone Fair-Poor	No	Yes	This study was supported by Johnson & Johnson Pharmaceutical Research and Development	3 phases in the study, acute, continuation, and maintenance. Only patients who responded to initial treatment phase were randomized, Adverse events reported in 47.7% with risperidone; versus 36.2% with placebo in continuation phase of study. During the maintenance phase, 21% of Tx group and 22% were on concomitant psychostimulants, the effect of these on outcomes not assessed.
Snyder et al, 2002 Risperidone Conduct Study Group Canada, US, South Africa	Yes	Yes	Funded by Janssen Research Foundation	

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR) Biederman 2006 (post hoc subgroup analysis)	118	6 weeks	Double-blind, multicenter	Disruptive Behavior Disorders	Healthy and ages 5 to 12 years with symptoms sufficiently severe that the investigator felt there was a need for antipsychotic treatment; DSM-IV axis I diagnosis of conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified; and axis II diagnosis of subaverage IQ (36-84), and a Vineland Adaptive Behavior Scale score 84 or less. Total rating of 24 or higher on the conduct problem subscale of the Nisonger Child Behavior Rating Form. Individuals with attention deficit hyperactivity disorder were also eligible if they met all other inclusion criteria.
Buitelaar, 2001 The Netherlands (FAIR)	38	6 weeks	Double-blind, single center	Disruptive Behavior Disorders	Adolescent inpatients with subaverage cognitive skills. Included if their overt aggressive behavior persisted during hospitalization, as reflected in a score of at least 1 on the modified Overt Aggression Scale (OAS-M) rated by nurses in the ward at the end of the baseline phase; their aggressive behavior failed to responds to behavioral treatment approaches; there was a clinical indication for drug treatment; they were between 12 and 18 years old; they had a principal diagnosis of conduct disorder, oppositional defiant disorder, or ADHD according to DSM-IV, and a full-scale IQ between 60 and 90 on the WISC-R.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Run-in/washout period
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR) Biederman 2006 (post hoc subgroup analysis)	Diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorder; head injury as a cause of intellectual disability; or a seizure disorder requiring medication. Known hypersensitivity to risperidone or neuroleptics, history of tardive dyskinesia or neuroleptic malignant syndrome, serious or progressive illnesses, presence of HIV, and use of an investigational drug within the previous 30 days; previous treatment with risperidone.	Risperidone mean dose 1.16 mg/day (range 0.006-0.092 mg/kg/day)	1-week placebo run-in to rule out placebo responders.
Buitelaar, 2001 The Netherlands (FAIR)	Neurologic, cardiac, pulmonary, or hepatic diseases, primary mood disorders, schizophrenia or other active psychosis, or suicidality, comorbid substance abuse disorder according to DSM-IV; if female, pregnant or used inadequate contraception; major change in treatment strategy (such as transition to another ward) was expected in the near future; or it was not considered feasible to discontinue current psychotropic medication.	risperidone 1 mg or placebo	no run-in; 2 week washout after double-blind period.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR) Biederman 2006 (post hoc subgroup analysis)	Use of other antipsychotics, anticonvulsants, antidepressants, lithium, carbamazepine, valproic acid, or cholinesterase inhibitors was not permitted. Use of consistent doses of psychostimulants permitted if the dose had been stable for at least 30 days. Behavioral therapy permitted if initiated at least 30 days before the start of the study. No changes to psychostimulant use or behavioral therapy were allowed, no medications for sleep or anxiety were to be initiated during the trial. Subjects receiving antihistamines, chloral hydrate, or melatonin for sleep before the screening visit could continue use unchanged. Medications commonly used to treat EPS were discontinued at study entry. If EPS arose during the study, dose of study medication was decreased. If this resulted in deterioration of conduct disorder symptoms or failed to improve the EPS, anti-EPS medication could be considered.	Mean age 8 years (SD 2 years) 82% male 57% white, 34% black, 5% Hispanic, <1% Asian, 3% other ethnicity.	DSM-IV axis I diagnosis: 21% oppositional defiant disorder 32% oppositional defiant disorder plus ADHD 18% conduct disorder 22% conduct disorder plus ADHD 2% disruptive behavior disorder not otherwise specified 5% disruptive behavior disorder plus ADHD DSM-IV axis II diagnosis: 51% borderline intellectual disability 32% mild intellectual disability 17% moderate intellectual disability
Buitelaar, 2001 The Netherlands (FAIR)	Concomitant medication for acute or chronic somatic illnesses was allowed at the discretion of the clinician in charge.	14.0 86.8% male Ethnicity NR	Principal diagnosis: Conduct disorder: 78.9% Oppositional defiant disorder: 15.8% Disruptive behavior disorder NOS: 5.3%

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales	Method of outcome assessment and timing of assessment
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR) Biederman 2006 (post hoc subgroup analysis)	142 screened/119 eligible/118 enrolled	12 risperidone, 19 placebo patients withdrew, 115 analyzed (3 in risperidone group had no efficacy data, not analyzed).	Primary outcome: Conduct problem subscale of the Nisonger Child Behavior Rating From problem behaviors section. Secondary measures: Other Nisonger Child Behavior Rating From problem behaviors section subscales and the social competence section subscales; Aberrant Behavior Checklist subscale scores, investigator's rating on the CGI severity scale, and CGI change scores. Change in a VAS rating of an individual target symptom for each patient (the symptoms considered most disturbing for the patient and his/her surroundings) was evaluated.	Method not reported; visits scheduled on day 0 (initiation of treatment), days 7, 14, 21, 28, 35, and 42 (final visit).
Buitelaar, 2001 The Netherlands (FAIR)	145/48/38	2 (placebo)/NR/38	CGI-Severity Secondary measures: OAS-M, ABC.	CGI-S at selection, end of baseline period, 2, 4, 6 weeks (endpoint), and end of washout period

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment	Overall withdrawals/ Withdrawals due to AEs
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR)	Change in Nisonger Child Behavior Rating Form conduct problem subscale score at 6 weeks (risperidone vs placebo): -15.2 vs -6.2 (p<0.001)	Physical examinations and electrocardiograms at screening and at the end of treatment. Measures of cognitive function were performed at baseline and endpoint. Weekly safety assessments included a visual analogue scale rating of sedation, Extrapyramidal Symptom Rating Scale scores for the severity of extrapyramidal symptoms, and measures of vital signs and weight.	3/118 (2.5%)/ 2/118 (1.7%)
Biederman 2006 (post hoc subgroup analysis)	CGI change score (risperidone vs placebo): improved: 76.9% vs 33.4% (p<0.0001) much to very much improved: 7.9% vs 53.8% (p<0.001) Biederman 2006 analysis of affective symptoms: Risperidone effective in treating factors explosive irritability; agitated/expansive/grandiose; and depression. No difference from placebo on factors		
Buitelaar, 2001 The Netherlands (FAIR)	risperidone vs placebo Markedly or severely disturbed: 21% vs 84% Mean (SD) CGI-Severity score: 2.7 (1.2) vs 4.4 (1.0)	Extrapyramidal Symptoms Rating Scale; other adverse events elicited by investigator	2 overall/ 0 due to AEs

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Adverse events
Aman et al, 2002 Risperidone Disruptive Behavior Study Group US (FAIR)	No serious adverse events Most common adverse events, placebo vs risperidone: somnolence:10% vs 51%, headache: 14% vs 29%, vomiting: 6% vs 20%, dyspepsia: 6% vs 15%, weight increase: 2% vs 15%, elevated serum prolactin: 2% vs 13%, increased appetite: 6% vs 11%, and rhinitis: 5% vs 11%. Amount of weight gain not reported.
Biederman 2006 (post hoc subgroup analysis)	
Buitelaar, 2001 The Netherlands (FAIR)	Extrapyramidal symptoms were absent or very mild during risperidone treatment. Transient tiredness in 11/19 (58%) drug-treated subjects. Weight gain: mean 3.5% of body weight in risperidone group

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Connor 2008 USA	19	6 weeks plus 1 week screening	Double-blind, single center	Adolescents with conduct disorder	12 and 17 years inclusive and to meet criteria for a primary psychiatric diagnosis of conduct disorder; patients had to have a moderate-to-severe degree of aggressive behavior as documented by an overt aggression scale score > 25 and at least moderate severity of symptoms as documented by a Clinical Global Impressions–Severity (CGI-S) score > 4 .
Findling et al, 2000 US (FAIR)	20	10 weeks	Double-blind, single, inner-city, academic medical center.	Disruptive Behavior Disorders	Outpatients who met DSM-IV criteria for conduct disorder as a primary diagnosis; ages 5 to 15 years, with at least a moderate degree of overall symptom severity as based on the CGI Scale, and an Aggression subscale T score 2 SD or more above the mean for age- and gender-matched peers on the Child Behavior Checklist (CBCL).

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Run-in/washout period
Connor 2008 USA	Co-morbid psychiatric diagnosis of schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified(NOS), bipolar disorder, psychotic depression, or bipolar disorder NOS; alcohol or substance abuse or dependence within 3 months: significantly subaverage IQ ; lenticular abnormality or juvenile cataracts; seizure disorder; concurrent administration of any psychoactive medication, including stimulants; pregnant or lactating females; and any unstable medical disease	Mean quetiapine was 294 ± 78 mg/day (range 200–600 mg/day) vs.. Placebo	1-week washout for stimulants and a 4-week washout d for other psychoactive medications
Findling et al, 2000 US (FAIR)	Moderate or severe attention deficit/hyperactivity disorder, significant psychiatric comorbidity (including mood disorders), treatment with a psychotropic medication within one week of initiating double-blind therapy, a positive toxicology screen, suicide attempt within the past month, clinically significant general medical condition, organic mental syndromes, pregnant or nursing females, females of childbearing potential who were not using an acceptable method of birth control, and a standard score equivalent to <70 on the Peabody Picture Vocabulary Test-Revised.	Risperidone 0.25 mg if weight less than 50 kg; 0.50 mg if weight 50 kg or greater. Starting dose was 1 tablet per day; dose could be increased by 1 tablet per day each week to a maximum daily dose of 6 tablets per day. All dose adjustments were to occur during the first 6 weeks of the study.	None reported.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics
Connor 2008 USA	Oral benztropine was permitted for EPS.	Mean age 14.1 (1.6) yrs 74% male 76% Caucasian 16% Hispanic 10% African American	Conduct disorder 100% Oppositional defiant disorder (ODD) 95% ADHD 79%
Findling et al, 2000 US (FAIR)	For patients in whom EPS developed, treatment with oral benztropine was available.	Mean age 9.2 years (SD 2.9), range 6-14 19/20 (95%) male 50% white (no other ethnicity information reported)	9 patients had not improved with treatments with other psychotropic medications (methylphenidate). Other medications previously prescribed included dextroamphetamine (n=4), clonidine (n=3), an antidepressant (n=5), divalproex sodium (n=2), and thioridazine (n=1).

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales	Method of outcome assessment and timing of assessment
Connor 2008 USA	NR/68/20	8/0/19	CGI-S, OAS, CPRS-CP	Weekly
Findling et al, 2000 US (FAIR)	Number screened, eligible not reported/20 enrolled	4/10 risperidone, 6/10 placebo patients withdrew/1 placebo patient lost to followup/20 analyzed	Primary outcome: Rating of Aggression Against People and/or Property Scale (RAAPP) Secondary measures: CGI-S, CGI-I, Conners Parent Rating Scale (CPRS), Child Behavior Checklist (CBCL)	Method not reported; assessments weekly to week 10.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment	Overall withdrawals/ Withdrawals due to AEs
Connor 2008 USA	Baseline/endpoint CGI-S Quetiapine 5.9 (0.6) / 3.4 (1.1) Placebo 5.5 (1.2)/ 5.0 (0.6) OAS Quetiapine 73.2 (34.3) / 43.3 (55.6) Placebo 40.4 (23.8) / 49.4 (27.8) CPRS-CP Quetiapine 17.1 (5.1) / 11.3 (7.7) Placebo 11.4 (3.6) / 12.2 (4.4) Q-LES-Q Quetiapine 36.9 (8.6) 48.2 (10.2) Placebo 39.3 (9.5) 35.2 (8.0)	General question method for the child and by parent-completed antipsychotic side effects rating scale and Neurological side effects were assessed weekly by the Neurological Rating Scale, the Barnes Akathisia Scale , and at baseline and final visit with the Abnormal Involuntary Movement Scale (AIMS)	8 overall 1 due to AEs
Findling et al, 2000 US (FAIR)	Rating of Aggression Against People and/or Property Scale (RAAPP) score Difference from baseline, weeks 7-10: risperidone: -1.91 placebo: -0.70 (p=0.0007) Difference from baseline, week 10: risperidone: -1.65 placebo: -0.16 (p=0.03) Mean CGI-I score at weeks 7-10: risperidone: 1.80 placebo: 3.19 (p=0.0006) Mean CGI-I score at week 10: risperidone: 1.80 placebo: 3.60 (p=0.002)	Physical exam, Simpson Angus Scale, Barnes Akathisia Scale, AIMS, query of parents or guardians	5/17 (29.4%) withdrew overall, no withdrawals due to AEs

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Adverse events
Connor 2008 USA	Quetiapine vs. placebo n (%) Agitation 6 (66) vs. 9 (90) Anxiety 6 (66) 7 vs. (70) Decreased energy 3 (33) vs. 5 (50) Decreased mental alertness 3 (33) vs. 9 (90) P = 0.01 Diminished emotional expression 1 (11) vs. 7 (70) P = 0.009 Diminished facial expression 1 (11) vs. 6 (60) P = 0.03 Drooling 2 (22) vs. 0 (0) Irritability 7 (78) vs. 8 (80) Muscle stiffness 1 (11) vs. 2 (20) Overeating 1 (11) vs. 2 (20) Pacing 4 (44) vs. 5 (50) Restlessness 7 (78) vs. 7 (70) School refusal 2 (22) vs. 4 (40) Sedation 6 (67) vs. 9 (90) Social withdrawal 4 (44) vs. 5 (50) Tremor 0 (0)0 vs. 3 (30) Weight gain 3 (33) vs. 1 (10)
Findling et al, 2000 US (FAIR)	No extrapyramidal symptoms

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Hollander, 2006 US (FAIR)	11	8 weeks	Double-blind, RCT, single center	Children and adolescents with pervasive developmental disorders	Between ages of 6 and 17 years, fulfilling DSM-IV and ADI-R criteria with a rating of at least moderate (4 or greater) on the CGI. Patients were not selected for particular scores of aggressive or disruptive behaviors on study measures.
Luby, 2006 US (FAIR)	24	6 months	Double-blind, RCT, single center	Preschool children with autism spectrum disorders	Preschool children between age 2.5 and 6.0 years who met DSM-IV criteria for autism or PDD-NOS, previously diagnosed and referred by a clinician.
Nagaraj, 2006 India (FAIR)	40	6 months	Double-blind, RCT, single center	Children with autism	Consecutive children up to 12 years of age, diagnosed with autism according to the DSM-IV criteria. Referred with varying symptoms, including hyperactivity, aggression, stereotypes, and language difficulties.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Run-in/washout period
Hollander, 2006 US (FAIR)	Patients who were responding well to prior pharmacological treatment; psychotic disorders and a history of any clinically significant medical illness (with the exception of a stable seizure disorder).	Olanzapine, titrated according to weight up to a maximum of 20 mg/day vs placebo Mean doses 10 (SD 2.04) mg/day; range 7.5 mg-12.5 mg	Patients were required to be free of psychotropic medications for at least 4 weeks prior to starting the study drug with the exception of stable dose (at least 3 months) of anticonvulsants for seizures or clonidine or chloral hydrate given only at bedtime for sleep.
Luby, 2006 US (FAIR)	Other known significant CNS disorders; significant medical problems or other psychiatric disorders requiring pharmacotherapy.	Risperidone 0.5-1.5 mg or placebo Mean dose 1.14 mg (SD 0.32)	NR
Nagaraj, 2006 India (FAIR)	Severe mental retardation, any significant coexisting disease or illness (neurologic, cardiovascular, respiratory, genetic), or severe malnutrition (weight for age <60% of National Center for Health Statistics median)	risperidone 1 mg vs placebo	1-month washout of psychoactive medications

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics
Hollander, 2006 US (FAIR)	None of the patients was taking any concomitant medications during the study.	Mean age 9.1 years (range 6.0-14.8) 81.8% male 63.6% white, 18.2% black, 9.1% Hispanic, 9.1% Asian	6/11 autism, 1 Asperger's syndrome, 4 PDD-NOS 36.4% normal cognitive functioning, 45.5% mild mental retardation, 0% moderate, 18.2% severe, 0% profound
Luby, 2006 US (FAIR)	Participating families were strongly encouraged to minimize the use of adjunctive medications and/or supplements (hormones, vitamins, diets) over the duration of treatment.	49 months 17/23 male (73.9%) 92% Caucasian	All were receiving behavioral therapy (risperidone 21.2 hours per week, placebo 11.3 hours per week; p=0.13)
Nagaraj, 2006 India (FAIR)	None	Mean age 5 years 92.3% male	43.6% borderline IQ, 28.2% mild mental retardation, 28.2% moderate mental retardation

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales	Method of outcome assessment and timing of assessment
Hollander, 2006 US (FAIR)	20/NR/11	3/0/NR	CGI-I CY-BOCS OAS-M irritability measure OAS-M aggression measure	Clinician-rated at 8 weeks
Luby, 2006 US (FAIR)	NR/NR/24	1/NR/23	Childhood Autism Rating Scale Gilliam Autism Rating Scale Vineland Adaptive Behavior Scales, Interview Edition Childhood Behavior Checklist Preschool Language Scale, Third Edition Additional developmental assessment using standardized and experimental cognitive, neuropsychological, and observational measures	Clinician observation, parent report at baseline, 2, 4, and 6 months
Nagaraj, 2006 India (FAIR)	NR/NR/40	1/0/39	CARS Children's Global Assessment Scale	Investigator-assessed; baseline, and every 8 weeks until end of 6-month period.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment	Overall withdrawals/ Withdrawals due to AEs
Hollander, 2006 US (FAIR)	Response on CGI-I: 50% risperidone and 20% placebo No evidence for significant change on other outcome measures	Recorded from each subject at each visit using the Olanzapine Side Effect Checklist AIMS, Simpson Angus Scale, and Barnes Akathisia Scale	3 overall/ 0 due to AEs
Luby, 2006 US (FAIR)	CARS total score at endpoint: risperidone 33.0 (SD 4.3) placebo 31.5 (SD 5.1) p=0.059 Controlled for motor development: p=0.12 Controlled for language skills: p=0.67	Side effects and adverse events were monitored at each study visit by the child psychiatrist, who was not blind to treatment condition.	0/0
Nagaraj, 2006 India (FAIR)	CARS: 63% risperidone vs 0% placebo had improvement of at least 20% Median score (range) at end of treatment, risperidone vs placebo: 39.5 (32.5-46) vs 38.5 (31.5-43); p<0.001 Children's Global Assessment Scale Score: 89% risperidone vs 10% placebo had improvement of at least 20% Mean score (SD) at end of treatment, risperidone vs placebo: 40.94 (7.83) vs 35.2 (9.38); p=0.035	Physical exams, 24-hour telephone number made available to parents to report any AEs or unexpected outcomes.	1 withdrew/ 0 due to AEs

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Adverse events
Hollander, 2006 US (FAIR)	Weight gain: 7.5 (SD 4.8) lbs olanzapine vs 1.5 (SD 1.5) lb placebo; p=0.028 66.6% olanzapine vs 20% placebo subjects had a more than 7% weight gain. Most common side effects were increased appetite and sedation No abnormal movements, dyskinesias, or EPS
Luby, 2006 US (FAIR)	No deaths or serious treatment-related adverse events. Mean weight change (SD) from baseline to endpoint, risperidone vs placebo: 2.96 kg (2.53) vs 0.61 kg (1.10); p=0.008. Most common adverse events were transient sedation (n=5), increased appetite (n=6), and hypersalivation (n=2). One child had transient staring spells and periods of apparent waxy flexibility (after minor head injury, not attributed to medication)
Nagaraj, 2006 India (FAIR)	Increased appetite and improved eating habits in 17/19 children receiving risperidone (89.5%) Mean weight change, risperidone vs placebo: 2.81 kg (SD 2.04, 17% increase) vs 1.71 kg (1.3, 9.3% increase); NS

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Reyes, 2006 International [8 countries, non-US] Risperidone (FAIR-POOR)	335	6 months	Randomized, single-blind, multicenter; Maintenance vs withdrawal	Children and adolescents with disruptive behavior disorders who had responded to risperidone treatment over 12 weeks	Children and adolescents (ages 5-17 years) without moderate or severe intellectual impairment (IQ>=55), who met DSM-IV criteria for conduct disorder, oppositional defiant disorder, or disruptive behavior disorder not otherwise specified, with the diagnosis confirmed by the K-SADS-PL. Inclusion required that the conduct problem be serious enough to warrant clinical treatment with risperidone and be associated with a score >+24 on the conduct problem subscale of the Nisonger Child Behavior Rating Form-parent version at both screening and treatment initiation. Children and adolescents with comorbid ADHD were not excluded.
RUPP Trial McCracken, 2002 Arnold, 2003 Aman 2005 US (FAIR)	101	8 weeks	Double-blind, multicenter.	Autism	Ages 5 to 17 years, weight at least 15 kg, mental age of at least 18 months; meeting criteria for autistic disorder described in DSM-IV, with tantrums, aggression, self-injurious behavior, or a combination of these.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Run-in/washout period
Reyes, 2006 International [8 countries, non-US] Risperidone (FAIR-POOR)	Serious medical or psychiatric conditions such as schizophrenia or bipolar disorder.	risperidone vs placebo (maintenance vs withdrawal). Flexible dose depending on body weight. Maximum dose 0.75 mg (patients <50 kg) or 1.5 mg (those >=50 kg)	6 week open-label acute treatment period, 6-week single-blind treatment.
RUPP Trial McCracken, 2002 Arnold, 2003 Aman 2005 US (FAIR)	Serious medical disorders and other psychiatric disorders requiring medication; receiving a psychotropic drug that was deemed effective for the treatment of aggression, tantrums, or self-injurious behavior.	Children 20 to 45 kg: risperidone 0.5 mg, increased to 1 mg on day 4. Dose gradually increased in 0.5 mg increments to a maximum of 2.5 mg per day by day 29 Children over 45 kg: slightly accelerated dose schedule used, maximum dose of 3.5 mg. Children less than 20 kg: initial dose 0.25 mg. Scheduled dose increases could be delayed because of adverse effects or because of marked improvement at a lower dose. Dose reductions to manage side effects were allowed at any time, but there were no dose increases after day 29.	Ineffective medications gradually withdrawn, drug-free interval of 7 to 28 days, depending on the drug, was required before enrollment.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics
Reyes, 2006 International [8 countries, non-US] Risperidone (FAIR-POOR)	Concomitant therapy with stable psychostimulant dosing was permitted. Treatment with additional antipsychotics, lithium, anticonvulsants, or antidepressants was not permitted.	Mean age 10.9 years 86.6% male 87% Caucasian	36.7% Conduct disorder, 60.9% Oppositional defiant disorder, 2.4% Disruptive behavior disorder, NOS
RUPP Trial McCracken, 2002 Arnold, 2003 Aman 2005 US (FAIR)	Treatment with an anticonvulsant agent for seizure control was allowed if the dose had been unchanged for at least 4 weeks and if there had been no seizures for at least 6 months.	Mean age 8.8 (SD 2.7), range 5-17 81% male 66% white, 11% black, 7% Hispanic, 8% Asian, 8% other ethnicity	Mental development (risperidone vs placebo) Average or above-average IQ: 7% vs 4% Borderline IQ: 17% vs 9% Mild or moderate retardation: 43% vs 51% Severe retardation: 33% vs 36% (NS)

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales	Method of outcome assessment and timing of assessment
Reyes, 2006 International [8 countries, non-US] Risperidone (FAIR-POOR)	575/NR/335	49/0/335	Primary outcome: time to symptom recurrence, defined as deterioration of 2 or more points on the CGI severity scale or 7 or more points on the conduct problem subscale at two consecutive visits 6-8 days apart. Secondary efficacy measures: rates of discontinuation due to symptom recurrence, change from screening or baseline on the Nisonger Child Behavior Rating Form subscales, CGI severity and change scales, and VAS rating of the most troublesome symptom.	Assessed monthly during maintenance treatment
RUPP Trial McCracken, 2002 Arnold, 2003 Aman 2005 US (FAIR)	270 screened/158 eligible/101 enrolled	18 withdrawn/3 lost to followup/101 analyzed/	Primary outcomes: Aberrant Behavior Checklist (Irritability subscale), CGI-Improvement (CGI-I) Children who had at least a 25% reduction in the Irritability score and a rating of much improved or very much improved on the CGI-I scale were considered to have a positive response. Other outcomes: other subscales of the Aberrant Behavior Checklist (Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech)	Irritability scale based on ratings by parent or primary caregiver, CGI-I determined by clinical evaluator, at baseline and 8 weeks.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment	Overall withdrawals/ Withdrawals due to AEs
Reyes, 2006 International [8 countries, non-US] Risperidone (FAIR-POOR)	Risperidone vs placebo Time to symptom recurrence shorter with placebo (p=0.002) Symptom recurrence occurred in 25% of patients after 119 days with risperidone vs 37 days with placebo Rate of symptom recurrence: 27.3%, N=47 vs 42.3%, N=69 (p=0.002) Change from beginning to end of maintenance phase: Mean (SD), risperidone vs placebo Nisonger Child Behavior Rating Form Conduct problems: 5.0 (9.5) vs 8.8 (11.2); p<0.001 Insecure/anxious: 1.9 (6.2) vs 2.7 (6.5); p=0.20 Hyperactive: 0.8 (4.4) vs 2.4 (5.4); p=0.007 Self-injury/stereotypic behavior: 0.3 (1.5) vs 0.5 (1.8); p=0.34 Self-isolated/ritualistic: 0.8 (2.6) vs 0.9 (2.8); p=0.67 Overly sensitive: 0.4 (2.8) vs 1.0 (3.19); p=0.054 Compliant/calm: -1.5 (3.8) vs -2.8 (4.4); p<0.001 Adaptive/social: -0.9 (2.5) vs -1.7 (2.9); p=0.006 VAS rating of most troublesome symptom: 7.2 (26.9) vs 14.1 (27.8); p=0.01 CGI Severity: 0.6 (1.2) vs 1.2 (1.4); p<0.001 CGI Change: 3.6 (1.8) vs 4.3 (1.9); p<0.001 Children's Global Assessment Scale score: -3.5 (12.4) vs -10.2 (14.5); p<0.001	Spontaneous reporting of adverse events; cognitive function, laboratory values, ECG, and vital signs measured at screening and completion of continuation and maintenance phases; physical exam at screening and end of maintenance treatment.	49/335 (14.6%)/ 8/335 (2.4%)
RUPP Trial McCracken, 2002 Arnold, 2003 Aman 2005 US (FAIR)	Change in mean Irritability score from baseline to 8 weeks risperidone: -14.9 (56.9% decrease) placebo: -3.6 (14.1% decrease) (p<0.001) Positive response (at least 25% improvement on Irritability subscale and rating of much improved or improved on CGI-I) risperidone: 34/49 (69%) placebo: 6/52 (12%) (p<0.001)	Lab tests, EKG, and physical exam at baseline, 8 weeks, weight and vital signs assessed weekly. At each visit, primary clinician inquired about health problems, intercurrent illness, and concomitant medications and administered 32-item questionnaire concerning energy level, muscle stiffness, motor restlessness, bowel and bladder habits, sleep, and appetite. Neurologic side effects assessed weekly with the Simpson-Angus scale and AIMS. Adverse events noted as a result of any of these methods were documented with respect to severity, duration, management, and outcome.	3/49 (6%) risperidone 18/52 (35%) placebo (p=0.001)/ No withdrawals due to AEs

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Adverse events
Reyes, 2006 International [8 countries, non-US] Risperidone (FAIR-POOR)	Most frequent adverse events were headache, rhinitis, URTI, pharyngitis, abdominal pain, somnolence, fatigue, increased appetite, and weight gain Risperidone vs placebo: Serious adverse events: 3.5% vs 3.1% Weight gain: 1.2% vs 0.6% Mean weight gain from beginning to end of maintenance phase: 2.1 kg (SD 2.7) vs -0.2 kg (SD 2.2)
RUPP Trial McCracken, 2002 Arnold, 2003 Aman 2005 US (FAIR)	Mean weight gain at 8 weeks: risperidone: 2.7 kg (SD 2.9) placebo: 0.8 kg (SD 2.2) (p<0.001) No extrapyramidal symptoms in either group. No serious adverse events in risperidone group. Parents reported 5 neurological side effects, of these, tremor was significantly more common in the risperidone group (p=0.06) 60 different adverse events recorded, 29 of which occurred in 5% or more of patients. Adverse events with a significantly different incidence (risperidone vs placebo) Increased appetite (mild): 49% vs 25% (p=0.03) Increased appetite (moderate): 24% vs 4% (p=0.01) Fatigue: 59% vs 27% (p=0.003) Drowsiness: 49% vs 12% (p<0.001) Drooling: 27% vs 6% (p=0.02) Dizziness: 16% vs 4% (p=0.05)

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Shea, 2004 Canada (FAIR)	80	8 weeks	Double-blind, multicenter	Pervasive developmental disorders	Physically healthy male and female outpatients ages 5 to 12 years with a DSM-IV Axis I diagnosis of pervasive developmental disorder and a total score of 30 or more on the Childhood Autism Rating Scale (CARS), with or without mental retardation.
Pandina, 2007 Canada Subgroup analysis of Shea, 2004 Previously included as an abstract only (FAIR)	55	8 weeks	Double-blind, multicenter	Children with autism	Physically healthy male and female outpatients ages 5 to 12 years with a DSM-IV of autistic disorder and a total score of 30 or more on the Childhood Autism Rating Scale (CARS).

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Run-in/washout period
Shea, 2004 Canada (FAIR)	Schizophrenia, other psychotic disorders, clinically relevant nonneurologic disease, clinically significant laboratory abnormalities, or a seizure disorder for which they were receiving >1 anticonvulsant or if they had had a seizure in the last 3 months. History of hypersensitivity to neuroleptics, tardive dyskinesia, neuroleptic malignant syndrome, drug or alcohol abuse, or HIV infection. Also excluded subjects who had used risperidone in the last 3 months, had been previously unresponsive or intolerant to risperidone, or were using a prohibited medication.	Risperidone oral solution 0.01 mg/kg/day on treatment days 1 and 2 and increased to 0.02 mg/kg/day on day 3. Depending on therapeutic response at day 8, the dose could be increased by a maximal increment of 0.02 mg/kg/day. Thereafter, the dose could be adjusted at the investigator's discretion at weekly intervals by increments/decrements not to exceed 0.02 mg/kg/day. The maximal allowable dose was 0.06 mg/kg/day. In case of drowsiness, the study medication could be administered once daily in the evening, or the total daily dose could be divided and administered on a morning and evening schedule.	None
Pandina, 2007 Canada Subgroup analysis of Shea, 2004 Previously included as an abstract only (FAIR)	Schizophrenia or other psychotic disorders; history of drug or alcohol abuse, tardive dyskinesia, neuroleptic malignant syndrome, seizure within the previous 3 months, or previous intolerance or unresponsiveness to risperidone.	Risperidone oral solution 0.01 mg/kg/day on treatment days 1 and 2 and increased to 0.02 mg/kg/day on day 3. Depending on therapeutic response at day 8, the dose could be increased by a maximal increment of 0.02 mg/kg/day. Thereafter, the dose could be adjusted at the investigator's discretion at weekly intervals by increments/decrements not to exceed 0.02 mg/kg/day. The maximal allowable dose was 0.06 mg/kg/day. In case of drowsiness, the study medication could be administered once daily in the evening, or the total daily dose could be divided and administered on a morning and evening schedule.	None

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics
Shea, 2004 Canada (FAIR)	Medications that are used to treat EPSs were to be discontinued at the time of entry into the trial. However, during the trial, anticholinergics could be initiated to treat emergent EPSs after the ESRS had been completed. Prohibited medications included antipsychotics other than the study medication, antidepressants, lithium, alpha-2 antagonists, clonidine, guanfacine, cholinesterase inhibitors, psychostimulants, and naltrexone. A single anticonvulsant and/or medications for sleep or anxiety were permitted only in the case in which the subject was already taking them at a stable dose for the 30 days before enrollment. Similar restrictions were placed on the use of behavior intervention therapy. Medications for preexisting organic disorders were allowed provided that the dose and schedule of administration were kept as constant as possible.	Mean age (range): 7.6 years (5-12) risperidone 7.3 years (5-12 placebo) 72.5% risperidone, 82.1% placebo males 15% risperidone, 15.4% placebo black; 67.5% risperidone, 71.8% placebo white; 17.5% risperidone, 12.8% placebo other race.	DSM-IV Axis I diagnosis, risperidone vs placebo: Autistic disorder: 67.5% vs 71.8% Asperger's disorder: 12.5% vs 17.9% Childhood disintegrative disorder: 2.5% vs 0% PDD not otherwise specified: 17.5% vs 10.3% 78% of risperidone and 90% of placebo patients had an IQ test performed. Of these (risperidone vs placebo): Normal, score > 85: 9.7% vs 31.4% Borderline, score 71-84: 19.4% vs 11.4% Mild, score 50-70: 38.7% vs 22.9% Moderate, score 35-49: 32.3% vs 34.3%
Pandina, 2007 Canada Subgroup analysis of Shea, 2004 Previously included as an abstract only (FAIR)	Medications that are used to treat EPSs were to be discontinued at the time of entry into the trial. However, during the trial, anticholinergics could be initiated to treat emergent EPSs after the ESRS had been completed. Prohibited medications included antipsychotics other than the study medication, antidepressants, lithium, alpha-2 antagonists, clonidine, guanfacine, cholinesterase inhibitors, psychostimulants, and naltrexone. A single anticonvulsant and/or medications for sleep or anxiety were permitted only in the case in which the subject was already taking them at a stable dose for the 30 days before enrollment. Similar restrictions were placed on the use of behavior intervention therapy. Medications for preexisting organic disorders were allowed provided that the dose and schedule of administration were kept as constant as possible.	Mean age 7.2 years 78.2% male 61.8% white, 18.2% black, 20% other race	0% risperidone vs 25% placebo patients had an IQ>84 (p=0.02); mean IQ (SD) 50.8 (19.8) risperidone vs 60.1 (26.9) placebo; p=0.213

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales	Method of outcome assessment and timing of assessment
Shea, 2004 Canada (FAIR)	NR NR 80	3 withdrawn/0 lost to followup/77 analyzed	Aberrant Behavior Checklist, Nisonger Child Behavior Rating Form (parent version), Visual Analog Scale for the most troublesome symptom, and the CGI-C.	Efficacy assessments scored at each clinic visit (baseline/screening, and end of treatment weeks 1, 2, 3, 5, 7, and 8).
Pandina, 2007 Canada Subgroup analysis of Shea, 2004 Previously included as an abstract only (FAIR)	NR NR 55	6/0/55/52	Aberrant Behavior Checklist, Nisonger Child Behavior Rating Form (parent version), Visual Analog Scale for the most troublesome symptom, and the CGI-C.	Efficacy assessments scored at each clinic visit (baseline/screening, and end of treatment weeks 1, 2, 3, 5, 7, and 8).

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment	Overall withdrawals/ Withdrawals due to AEs
Shea, 2004 Canada (FAIR)	Change from baseline to endpoint, risperidone vs placebo: ABC (Irritability): -12.1 vs -6.5 (p<0.001) ABC (Hyperactivity/noncompliance): -14.9 vs 7.4 (p<0.001) ABC (Inappropriate speech): -2.6 vs -1.6 (p<0.05) ABC (Lethargy/social withdrawal): -8.6 vs -5.7 (p<0.01) ABC (Stereotypic behavior): -4.3 vs -2.4 (p<0.05) N-CBRF (Conduct problem): -10.4 vs -6.6 (p<0.001) N-CBRF (Hyperactive): -8.1 vs -5.6 (p<0.05) N-CBRF (Self-isolated/ritualistic): -4.8 vs -3.6 (NS) N-CBRF (Insecure/anxious): -4.6 vs -3.5 (p<0.05) N-CBRF (Overly sensitive): -3.8 vs -2.7 (p<0.05) N-CBRF (Self-injurious/stereotypic): -2.6 vs -1.3 (NS) VAS (most troublesome symptom): -38.4 vs -26.2 (p<0.05) Improvement as assessed by the CGI-C: 87.2% vs 39.5%	Subjects attended clinic on 7 occasions: baseline screening visit and at the end of treatment weeks 1, 2, 3, 5, 7, and 8. Safety assessment measures, which included adverse event data, vital signs, and body weight, were collected at each visit. The presence and severity of EPSs were assessed at each visit by the investigator using the ESRS. A 12-lead EEG and routine biochemistry, hematology, and urinalysis were performed at baseline and at the end of treatment.	8.9% (2 risperidone, 5 placebo)/ 1 risperidone, 1 placebo.
Pandina, 2007 Canada Subgroup analysis of Shea, 2004 Previously included as an abstract only (FAIR)	Mean score at endpoint (SD), risperidone vs placebo; p-value for mean change between group difference): ABC (Irritability): 7.2 (5.9) vs 14.1 (11.3); p=0.002 ABC (Lethargy/social withdrawal): 4.7 (4.4) vs 8.2 (8.9); p=0.020 ABC (Stereotypic behavior): 3.9 (4.2) vs 6.9 (6.9); p=0.053 ABC (Hyperactivity/noncompliance): 13.3 (8.7) vs 26.4 (12.8); p=0.001 ABC (Inappropriate speech): 1.9 (2.2) vs 3.1 (3.5); p=0.058 N-CBRF (Adaptive/social): 5.3 (2.4) vs 4.3 (2.4); p=0.072 N-CBRF (Compliant/calm): 8.7 (3.3) vs 6.9 (2.9); p=0.072 N-CBRF (Conduct problem): 6.5 (5.7) vs 15.5 (11.9); p=0.0025 N-CBRF (Hyperactive): 9.4 (5.4) vs 14.9 (8.4); p=0.021 N-CBRF (Insecure/anxious): 3.2 (4.3) vs 5.4 (4.8); p=0.217 N-CBRF (Overly sensitive): 2.8 (2.3) vs 4.3 (3.3); p=0.029 N-CBRF (Self-injurious/stereotypic): 2.2 (3.1) vs 2.8 (3.9); p=0.0183 N-CBRF (Self-isolated/ritualistic): 2.4 (2.5) vs 4.5 (5.5); p=0.078 Change from baseline in VAS for most troublesome symptom (least squares mean estimate, SE): -40.2 (6.6) vs -24.9 (6.4); p=0.066 Improvement as assessed by the CGI-C: 58.3% vs 21.4% (p=0.008)	Adverse events, vital signs, weight, ESRS at every visit; biochemistry, hematology, urinalysis, and 12-lead ECG at baseline and endpoint.	2 of 55 (4%)/ 1 risperidone, 1 placebo

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Adverse events
Shea, 2004 Canada (FAIR)	Mean weight gain at 8 weeks: risperidone: 2.7 kg (SD 2.0) placebo 1.0 kg (SD 1.6) (p<0.001 vs placebo Most common adverse events among risperidone-treated subjects were somnolence (72.5%), upper respiratory tract infection (37.5%), rhinitis (27.5%), and increased appetite (22.5%). 5 (12.5%) risperidone-treated subjects experienced adverse events categorized as severe and related to study medication (1 hyperkinesia and somnolence and 1 case each of weight gain, somnolence, aggressive reaction with impaired concentration, and extrapyramidal disorder as a result of an accidental overdose). Five cases of mild to moderate tachycardia in the risperidone group were reported as adverse events. Changes from baseline in EKG recordings were deemed to be clinically important for one subject in risperidone group; changes included tachycardia and a possible mild conduction anomaly.
Pandina, 2007 Canada Subgroup analysis of Shea, 2004 Previously included as an abstract only (FAIR)	Mean weight (SD) at baseline and end point: risperidone: 30.4 (11.8); 32.8 (12.6) kg placebo: 27.3 (8.9); 28.4 (9.8) kg p=0.276 1 case of hyperkinesia and 1 case of extrapyramidal disorder in patients receiving risperidone.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	110	6 weeks	Double-blind, multicenter	Disruptive Behavior Disorders	DSM-IV diagnosis of conduct disorder, oppositional defiant disorder, or disruptive behavior disorder, not otherwise specified; rating (parent/caregiver) of 24 or higher on the Conduct Problem subscale of the Nisonger Child Behavior Rating Form (NCBRF); IQ between 36 and 84; Vineland Adaptive Behavior Scale score of 84 or less; healthy on the basis of a pretrial physical examination, medical history, and ECG; and consent by parent/caregiver.
Troost, 2005 The Netherlands	24	8 weeks (placebo-controlled discontinuation phase)	Double-blind, single center	Pervasive developmental disorders	DSM-IV criteria for a pervasive developmental disorder. Patients were required to demonstrate clinically significant tantrums, aggression, self-injurious behavior, or a combination of these problems. Age 5 to 17 years, a weight of at least 15 kg, and a mental age of at least 18 months. Only short-term responders to risperidone as judged within the first 8 weeks of treatment cold complete the protocol. Short-term response was defined as at least a 25% ABC Irritability score reduction and a rating of "much improved" or "very much improved" on the CGI-S.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Run-in/washout period
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	Diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorder; head injury as a cause of impaired IQ; seizure condition requiring medication; females who were sexually active without a reliable form of birth control; serious or progressive illness or clinically abnormal laboratory values; history of tardive dyskinesia, neuroleptic malignant syndrome, or hypersensitivity to any antipsychotic drug; known presence of HIV; and previous treatment with risperidone.	Risperidone oral solution beginning at 0.01 mg/kg for the first 2 days and at 0.02 mg/kg for the next 5 days. Physician could increase the dosage weekly by 0.02 mg/kg per day to a maximum of 0.06 mg/kg per day, or decrease the dose by any amount for the remainder of the trial. 6 weeks	One week placebo run-in to rule out placebo responders.
Troost, 2005 The Netherlands	On effective psychotropic drug treatment for disruptive behavior	Children on effective psychotropic drug treatment for disruptive behavior were excluded.	7- to 28 day washout period to withdraw from ineffective medications.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	Patients taking previously prescribed stable dosages of concomitant medication (e.g., medication for preexisting medical conditions, psychostimulants for comorbid ADHD, and sleep medication [antihistamines, chloral hydrate, and melatonin]) for 30 days prior to trial entry were included provided the medication was expected to remain stable for the duration of the trial. No other medication was allowed with the exception of anticholinergic medication to treat EPS shout it occur during the trial.	Mean age 8.7 (SD 0.27) years 75% male 75% white, 7% black, 16% other ethnicity	DSM-IV diagnoses: 9% conduct disorder 31% conduct disorder plus ADHD 15% oppositional defiant disorder, destructive behavior disorder 53% oppositional defiant disorder, destructive behavior disorder plus ADHD 26% combined/no ADHD 76% combined plus ADHD 48% borderline IQ (70-85) 38% mild mental retardation (IQ 50-69) 14% moderate mental retardation (IQ 35-49)
Troost, 2005 The Netherlands	Anticonvulsants used for the treatment of a seizure disorder were permitted if the dose had been stable for at least 4 weeks and the patient was seizure free for at least 6 months.	Mean age 9.1 years 91.7% male 91.7% white, 0% black, 8.3% other race	25% Autistic disorder, 8.3% Asperger's disorder, 66.7% pervasive developmental disorder, NOS

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome scales	Method of outcome assessment and timing of assessment
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	Number screened not reported/133 eligible/110 enrolled (23 placebo responders not randomized)	24 withdrawn/1 lost to followup/110 analyzed	Primary outcome: Conduct problem subscale of the Nisonger Child Behavior Rating. Secondary measures: Subscales on the ABC, the Behavior Problems Inventory (BPI), CGI, Visual Analogue Scale of most troublesome symptoms, and Visual Analogue Scale of sedation.	Each child rated weekly (by parents?) at baseline, weeks 1, 2, 3, 4, 5, and 6 on NCBRF, ABC, BPI, CGI, ESRS, VAS/Sedation, and VAS/symptom. Cognitive function assessed at baseline and at the end of week 6.
Troost, 2005 The Netherlands	36 entered 8-week open label phase/26 classified as responders after 24-week open-label treatment/24 enrolled in 8-week discontinuation phase	2 withdrew before randomization in discontinuation phase 24 analyzed	Primary outcome: Difference in relapse rate between groups, defined as CGI-C scores of "much worse" or "very much worse" for at least 2 consecutive weeks when compared with baseline of the discontinuation phase, and a minimum increase of 25% in Irritability scores on the most recent Aberrant Behavior Checklist (ABC).	See Outcome Scales

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Results	Method of adverse effects assessment	Overall withdrawals/ Withdrawals due to AEs
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	Change in Nisonger Child Behavior Rating Form conduct problem subscale score at 6 weeks (risperidone vs placebo): -15.8 vs -6.8 (p<0.001)	Extrapyramidal Symptoms Rating Scale	24 overall
Troost, 2005 The Netherlands	3/12 (25%) risperidone vs 8/12 (67%) placebo relapsed (p=0.049) Increase in ABC Irritability scores at study endpoint: 14% risperidone vs 60% placebo (p=0.043). No differences between groups in other ABC subscales.	Routine laboratory tests, electrocardiography, and physical examination before treatment, at weeks 8 and 24, and at study end. Weight and vital signs assessed weekly in the discontinuation phase. Neurological side effects assessed with the Simpson-Angus Scale and the Abnormal Involuntary Movement Scale. Adverse events documented with respect to severity, duration, management, and outcome.	2 for unacceptable weight gain

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Adverse events
Snyder et al, 2002 Risperidone Conduct Study Group Canada (FAIR)	Most common side effects included somnolence, headache, appetite increase, and dyspepsia. Side effects related to extrapyramidal symptoms were reported in 7 (13.2%) and 3 (5.3%) of the subjects in the risperidone and placebo groups, respectively (p = .245)
Troost, 2005 The Netherlands	Increased appetite and weight gain (5.7 ± 2.8 kg in 24 weeks, range 1.2–11.7 kg; p < .0001). No changes on Simpson-Angus scale or AIMS. Neurological side effects included tremor (once), muscle rigidity (twice), and restlessness (twice).

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Biederman 2005 USA	Open-label, randomized if they had not received treatments previously, however if they had then they were put on the other. Single center	Male or female subjects, aged 4–6 years, DSM-IV bipolar I disorder, DSM-IV bipolar II disorder, or bipolar disorder not otherwise specified (NOS) and were currently displaying manic, hypomanic, or mixed symptoms (with or without psychotic features)	Risperidone mean 1.4± 0.5 mg/day, Olanzapine mean 6.3±2.3 mg/day.
Delbello 2002 USA	DB RCT Single center	12–18 years old, met DSM-IV criteria for bipolar I disorder currently mixed or manic, and had a Young Mania Rating Scale (YMRS) score of ≥20.	Adjunctive to divalproex (DVP) quetiapine, 450 mg/day or placebo 6 weeks

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Biederman 2005 USA	None	Stimulants if on stable dose for at least 30 days (none were on this), benztropine mesylate for EPS and lorazepam	YMRS and the CGI-I Response was defined by having either a 30% reduction in symptoms according to the YMRS at end point or by having been judged as much or very much improved on the CGI-Improvement - weekly assessments. the CDRS and the BPRS were assessed at baseline, week 4, and week 8	Mean age 5 yrs 71% male 97% Caucasian
Delbello 2002 USA	None	2 mg of lorazepam per day	YMRS; PANSS-P, Children's Depression Rating Scale (CDRS). Overall level of functioning at baseline and endpoint with Children's Global Assessment Scale (CGAS) by a child and adolescent psychiatrist with previously established reliability for each rating scale. Efficacy and safety ratings were performed at baseline, days 3 and 7, and then weekly until day 42 or termination	Mean age 14.3 years % male 53 % Caucasian 83

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Biederman 2005 USA	27 met criteria for bipolar I disorder and 4 met criteria for bipolar disorder NOS Mania 100% Major depression 73% Conduct disorder 42% ADHD 94%	NR/NR/31	7 (6 olanzapine, 1 risperidone)/2 LTF/31
Delbello 2002 USA	% mixed 77 % psychosis 47 % ADHD 60	50/30/30	7 (DVP+quetiapine 6, DVP+placebo 1) withdrawals, 0 LTF (though one moved away), 30 analyzed

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Biederman 2005 USA	Risperidone vs. olanzapine YMRS 30% reduction 69% vs. 53% P = 0.4 YMRS 50% reduction 53% vs. 33% P = 0.3 Risperidone baseline/endpoint vs. olanzapine baseline/endpoint **YMRS** 35.2(8.2)/16.4(12.0) vs. 34.2(6.4)/22.1(8.3) P = 0.2 Increased motor activity 3.5(.5)/1.8(1.5) vs. 3.3(.5)/ 2.7(1.2) P = 0 .04 Pressured speech 5.1(1.4)/2.7(2.0) vs. 4.5(1.9)/3.7(2.1) P = 0.04 **BPRS** 46.4(12.4)/33.3(10.6) vs. 46.7(13.5)/37.8(11.9) P = 0.4 **CDRS** 39.7 10.5 27.0 6.3a 42.4 14.8 34.1 11.5 F(1,30) .8, p .4	Spontaneous reports of treatment-emergent adverse effects, changes in vital signs and laboratory measures.
Delbello 2002 USA	DVP + quetiapine group vs. DVP + placebo YMRS response rate 87% vs. 53% P = 0.05 Other results reported graphically and there were no between group differences	Simpson-Angus, Barnes Akathisia , and Abnormal Involuntary Movement Scales Laboratory tests Vital signs, electrocardiograms (ECGs), physical and slit-lamp ocular examinations at baseline and endpoint. Adverse events were assessed when ratings were obtained by asking the adolescents and their primary caregivers open-ended questions about potential side effects

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Biederman 2005 USA	Results shown in graph, authors state, "...the rate of spontaneously reported side effects did not differ between risperidone- and olanzapine treated subjects. In both groups, the most commonly reported side effects were increased appetite, common cold symptoms, headaches, and sedation."	7 withdrawals (olanzapine 6 vs.. Risperidone 1 P = 0.03) 1 due to AEs	
Delbello 2002 USA	DVP + quetiapine group vs. DVP + placebo Change in EPS ratings, mean (SD) AIMS 0 (0) vs. 0 (0) Barnes Akathisia Scale –0.1 (0.3) vs. 0.1 (0.3) Simpson-Angus Scale 0 (0.8) vs. –0.1 (1.1) Sedation 12 (80) vs. 5 (33) P = 0.03 Nausea/vomiting 4 (27) vs. 6 (40) Dizziness 5 (33) vs. 3 (20) Headache7 (47) vs. 7 (47) Gastrointestinal irritation 7 (47) vs. 5 (33) Joint pain 2 (13) vs. 2 (13) Dry mouth 5 (33) vs. 2 (13	7 withdrawals , none due to AEs	

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
DelBello, 2009 USA	DB RCT two-site study	Adolescents (ages 12-18 years) with a depressive episode associated with bipolar I disorder according to DSM-IV, text revised and determined by the Washington University at St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia interview; screening and baseline Children's Depression Rating Scale-Revised Version score ≥ 40, a standard score that is considered consistent with clinically significant depression	Quetiapine vs Placebo 8 weeks 100 mg quetiapine IR (or placebo) on Day 1, 300 mg/day on Day 3, with flexible titration to 600 mg/day in the evening

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
DelBello, 2009 USA	None	The use of lorazepam (a maximum of 4 mg/day for Days 0-7 and 2 mg/day for Days 8-14) was permitted during the study for agitation or anxiety.	Children's Depression Rating Scale-Revised Version; Hamilton Anxiety Rating Scale; YMRS; Clinical Global Impression Bipolar Disorder Version Severity scores for overall illness; assessments performed on Days 0, 7, 14, 21, 28, 35, 42, 49, and 56.	Quetiapine vs Placebo Mean age (SD): 16 (2) vs 15 (2) years Females: 71% vs 67% White: 82% vs 80%

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
DelBello, 2009 USA	Quetiapine vs Placebo Length of current episode (SD): 7 (2) vs 5 (4) weeks Age at onset of bipolar disorder (SD): 12 (2) vs 11 (3) years Psychosis: 12% vs 7% ADHD: 12% vs 13% Anxiety disorders: 29% vs 20% Disruptive behavior disorders: 35% vs 13%	49/32/32	12/1 lost to FU/32

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
DelBello, 2009 USA	Quetiapine vs Placebo Mean change in Children's Depression Rating Scale-Revised Version score (SD): -19 (14) vs -20 (17); *P*=0.89 Change in Hamilton Anxiety Rating Scale: -4 vs -5; *P*=0.74 Change in YMRS: -5 vs -4; *P*=0.76 Change in Clinical Global Impression Bipolar Disorder Version Severity scores for overall illness: -1.8 vs -1.6; *P*=0.9	Adverse events were recorded by asking patients and primary caregivers open-ended questions about potential side effects. Vital signs measured included height, weight, and orthostatic blood pressure and pulse. EPS were assessed using the Simpson-Angus, Barnes Akathisia, and AIMS. These were performed at baseline and each weekly visit. ECG performed at baseline and endpoint. Laboratory tests at baseline and endpoint.

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
DelBello, 2009 USA	Quetiapine (n=17) vs Placebo (n=15) GI upset: 11 (65%) vs 5 (33%) Sedation: 10 (59%) vs 5 (33%) Dizziness: 7 (41%) vs 1 (7%) Cold symptoms: 4 (24%) vs 3 (20%) Tooth pain: 3 (18%) vs 0 Headaches: 3 (18%) vs 5 (33%) Shortness of breath: 3 (18%) vs 0 Fast heart rate: 3 (18%) vs 0 Dry mouth: 2 (12%) vs 0 Increased appetite: 2 (12%) vs 0 Difficulty swallowing: 2 (12%) vs 0 Chest pain or pressure: 2 (12%) vs 0 Back and/or neck pain: 2 (12%) vs 5 (33%) EPS: NS between groups Mean change in prolactin levels (SD): 2.47 (8.53) vs 0.05 (4.27) ng/ml; *P*=0.3 Mean change in supine blood pressure (SD): 6 (9) vs -6 (9) mm Hg; *P*=0.001 Mean change in pulse (SD): 11 (13) vs -3 (11) beats/min; *P*=0.003	Total withdrawals: 12 Withdrawals due to AE: 2	The mean (SD) quetiapine dose at endpoint was 403 (133) mg/day. For placebo, the mean dose at endpoint was 413 (141) mg/day.

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Findling, 2009 USA	DB RCT multicenter (59 sites)	Aged 19 to 17 years with a confirmed DSM-IV diagnosis of bipolar I disorder with current maniac or mixed episodes, with or without psychotic features, and a YMRS total score ≥20 at baseline. Subjects with comorbid ADHD, conduct disorder, oppositional defiant disorder, or anxiety disorders (except posttraumatic stress disorder or obsessive-compulsive disorder) were eligible.	Aripiprazole 10mg/d vs Aripiprazole 30 mg/d vs Placebo 4 weeks

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Findling, 2009 USA	3-day medication washout period	Benzodiazepine and anticholinergic therapy was permitted as rescue medication and for extrapyramidal symptom relief, although not within 4 or 12 hours of efficacy or safety assessments, respectively.	YMRS; Children's Global Assessment Scale; Clinical Global Impressions Scale-Bipolar Version severity of mania, depression, and overall bipolar illness; Children's' Depression Rating Scale-Revised; an abbreviated version of the General Behavior Inventory; parent questionnaire on home behaviors version of the ADHD Rating Scale-Version IV. Assessments performed at screening, baseline, and at each scheduled weekly visit through week 4.	Mean age (SD): 13.4 (2.2) years Male: 53.7% White: 65.2%

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Findling, 2009 USA	Mean age at onset (SD): 12.1 (3.0) years Mean duration of bipolar disease (SD): 1.3 (2.2) years Mean YMRS total score (SD): 30.0 (6.5) Treatment with antipsychotics within past month: 12.2% Family history of bipolar I disorder: 44.3%	413/NR/296	59/11/289

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Findling, 2009 USA	Aripiprazole 10 mg vs Aripiprazole 30 mg vs Placebo Mean changes in YMRS total score from baseline: -14.2 vs -16.5 vs -8.2; *P*<0.001 for aripiprazole vs placebo Mean changes in CGAS score: 15.1 vs 17.3 vs 5.8; *P*<0.001 for aripiprazole vs placebo Mean changes in Clinical Global Impressions Scale-Bipolar Version severity score-mania: -1.6 vs -2.1 vs -0.8; *P*<0.001 for aripiprazole vs placebo Mean changes in Clinical Global Impressions Scale-Bipolar Version-depression: -0.9 vs -0.9 vs -0.6; *P*=NS Mean changes in Clinical Global Impressions Scale-Bipolar Version-overall bipolar illness: -1.6 vs -2.0 vs -0.8; *P*<0.001 for aripiprazole vs placebo Mean changes in Children's' Depression Rating Scale-Revised score: -7.2 vs -6.1 vs -4.9; *P*=NS Mean changes in General Behavior Inventory total scores-parent/guardian (mania): -9.9 vs -9.5 vs -4.0; *P*<0.001 for aripiprazole vs placebo Mean changes in General Behavior Inventory total scores-parent/guardian (depression): -5.9 vs -4.1 vs -3.8; *P*=0.04 for 10 mg vs placebo; *P*=NS for 30 mg vs placebo Mean changes in General Behavior Inventory total scores-patient (mania): -6.4 vs -6.6 vs -4.6; *P<0.05 for aripiprazole vs placebo* Mean changes in General Behavior Inventory total scores-patient (depression): -3.4 vs -3.3 vs -3.4; *P*=NS Mean changes in ADHD-Rating Scale-Version IV total scores: -12.5 vs -11.9 vs -3.7; *P*<0.001 for aripiprazole vs placebo	An independent data safety monitoring board prospectively reviewed AEs throughout the study; AEs were patient/guardian reported; investigators record self-injuries behaviors and documented any relationship to suicide attempts. Vital signs and measurements of height and weight were obtained at screening and baseline and at each scheduled visit. Physical examinations, ECGs, and laboratory tests performed at baseline and week 4. Simpson-Angus Scale, AIMS and BARS at screening, baseline and at each visit.

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Findling, 2009 USA	Aripiprazole 10mg vs Aripiprazole 30 mg vs Placebo Serious AEs: 5.1% vs 2% vs 5.2% Any AEs: 73.5% vs 27.3% vs 3.1% Any extrapyramidal symptom event: 23.5% vs 39.4% vs 7.2% Change in Simpson-Angus Scale scores: 0.6 vs 1.2 vs -0.1; *P*=0.03 for 10 mg vs placebo; *P<0.001 for 30 mg vs placebo* *Change from baseline on the physician-rated BARS and AIMS did not differ from placebo at week 4.* No deaths or suicides during the study. No clinically meaningful changes from baseline in fasting serum glucose, total cholesterol, triglycerides, HDL-cholesterol, heart rate, blood pressure, ECG parameters.	Total withdrawals: 59 Withdrawals due to AE: 12	AEs resulting in study discontinuation in the 10 mg group were fatigue (n=2), sedation (n=2), akathisia (n=1), aggression (n=1), and suicidal ideation (n=1). In the 30 mg group, extrapyramidal disorder (n=3), exacerbation of bipolar disorder (n=2), vomiting (n=1), dystonia (n=1), and somnolence (n=1) led to study withdrawal (1 subject discontinued because of aggression and fatigue). Anxiety (n=1) and exacerbation of bipolar disorder (n=1) were AEs leading to discontinuation in the placebo group.

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Haas, 2009 USA	DB RCT Multicenter (21)	Children and adolescents (10–17 years, inclusive) without known intellectual impairment were eligible for enrollment as inpatients or outpatients if they met criteria from the DSM-IV for bipolar I disorder, current episode manic or mixed, and were medically stable as determined by the investigator; scored ‡ 20 on the scale at screening and baseline	Dose-titration risperidone 0.5–2.5 mg/day, risperidone 3–6 mg/day, or placebo 3 weeks

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Haas, 2009 USA	Washout period of 5 half-lives or a maximum of 5 days for subjects taking any protocol-prohibited concomitant medications at the time of study enrolment.	Medications for treatment-emergent movement disorders [extrapyramidal symptoms (EPS)] were allowed. Use of sedatives/hypnotics such as lorazepam and diphenhydramine was allowed, but strictly for the control of agitation, irritability, restlessness, insomnia, and hostility during washout and the double-blind treatment phase (week 1 only).	Change in YMRS total score and clinical response rate (defined by ≥50% reduction in YMRS total score), the Clinical Global Impression–Bipolar (CGI-BP) scale, and the BPRS for Children; assessed at baseline and days 7, 14, and 21	Median age (range): 13 (10-17) years 49% male 77% White 17% Black or African American 4% Mixed 2% American Indian/ Native Alaskan 1% Asian

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Haas, 2009 USA	36% bipolar I disorder, manic episode (DSM-IV) 64% bipolar 1 disorder, mixed episode (DSM-IV) 50% ADHD 58% with euphoria/elation (YMRS) 70% with irritability (YMRS)	237/170/170	32/3/166

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Haas, 2009 USA	risperidone 0.5-2.5 mg/day vs risperidone 3-6 mg/day vs placebo Mean change in YMRS total score (SD): -18.5 (9.7) vs -16.5 (10.3) vs -9.1 (11.0); *P*<0.001 for both risperidone doses vs placebo Clinical response rate at endpoint: 59% vs 63% vs 26%; *P*=0.002 for risperidone 0.5-2.5 mg/day vs placebo; *P*<0.001 for risperidone 3-6 mg/day vs placebo Remission rates, defined as YMRS score ≤12: 43% vs 43% vs 16%	Safety and tolerability were assessed by adverse event (AE) monitoring. Serious AEs were recorded during the study and for the 30 days post completion. AEs were reported by the patient or by the patient's representative. EPS were assessed via the AIMS, SARS, and BARS. The following assessments were also performed: clinical laboratory tests (hematology, serum chemistry, and urinalysis) at screening, baseline, and on day 21; ECGs at screening, day 7, and day 21; and vital signs, including body weight and height measurements, at all study visits.

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Haas, 2009 USA	risperidone 0.5-2.5 mg/day vs risperidone 3-6 mg/day vs placebo Mean change in AIMS: -0.02 (0.43) vs -0.08 (0.59) vs 0.11 (1.39) Mean change in SAR-S: 0.3 (0.11) vs 0.10 (0.32) vs -0.04 (0.16) n(%) Total prolactin-related AEs: 2 (4) vs 3 (5) vs 1 (2) Total AEs: 45 (90) vs 58 (95) vs 44 (76) Somnolence: 21 (42) vs 34 (56) vs 11 (19) Headache: 20 (40) vs 23 (38) vs 19 (33) Fatigue: 9 (18) vs 18 (30) vs 2 (3) Abdominal pain: 9 (18) vs 9 (15) vs 3 (5) Dizziness: 8 (16) vs 8 (13) vs 3 (5) Rhinitis: 7 (14) vs 8 (13) vs 6 (10) Nausea: 8 (16) vs 8 (13) vs 4 (7) Vomiting: 6 (12) vs 6 (10) vs 4 (7) Dyspepsia: 8 (16) 3 (5) vs 2 (3) Agitation: 2 (4) vs 7 (11) vs 6 (10) Pharyngitis: 5 (10) vs 2 (3) vs 3 (5) Total serious AEs: 3 (6) vs 5 (8) vs 3 (5) Psychosis manic-depressive: 1 (2) vs 4 (7) vs 2 (3) Suicide attempt: 2 (4) vs 2 (3) vs 1 (2) Manic reaction: 0 vs 0 vs 1 (2) Allergic reaction 0 vs 1 (2) vs 0 Asthma: 1 (2) vs 0 vs 0 Bronchospasm: 1 (2) vs 0 vs 0	Total withdrawals: 32 Withdrawals due to AEs: 17	

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Study design Setting	Eligibility criteria	Therapy type Interventions Duration
Tohen 2007 USA and Puerto Rico	DB RCT Multicenter (24)	13-17 Years old, inpatient or outpatient, with manic or mixed bipolar episodes (with or without psychotic features)	Switch olanzapine (2.5–20.0 mg/day, mean 8.9 mg/day) or placebo. 3 weeks
Tramontina 2009 Brazil	DB RCT Single center	Children and adolescents were extensively assessed according to DSM-IV criteria for bipolar disorder comorbid with ADHD in acutely manic or in mixed states	Stand alone treatment Aripiprazole vs.. Placebo 6 weeks

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Run-in/washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Tohen 2007 USA and Puerto Rico	2-14 days washout/screening	No	YMRS, Clinical Global Impressions—Bipolar Version overall, severity of mania, or depression subscales ; Children's Depression Rating Scale—Revised; Attention Deficit Hyperactivity Disorder (ADHD) Rating Scale-IV—Parent Version	Mean age 15.3 53% male 70% Caucasian
Tramontina 2009 Brazil	None	No	Young Mania Rating Scale; the Swanson, Nolan, and Pelham Scale-Version IV; and weight also the Clinical Global Impressions-Severity of Illness scale, the Child Mania Rating Scale-Parental Version (CMRS-P), the Children's Depression Rating Scale-Revised, the Kutcher Adolescent Depression Scale, assessed weekly	Mean age 12 years 47% male 91% white

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Tohen 2007 USA and Puerto Rico	89% mixed 18% psychotic 36% ADHD 31% Oppositional defiant disorder	214/177/161	41/0/161
Tramontina 2009 Brazil	BP I 81% BP II 19% 37% psychosis	710/NR/43	2 withdrawn/ 0 LTF/ 43 analyzed

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Tohen 2007 USA and Puerto Rico	Olanzapine vs.. Placebo Mean change in - YMRS –17.65 versus –9.99, P < 0 .001 Clinical Global Impressions— Bipolar Version overall –1.63 versus –0.99, P < 0.001 Clinical Global Impressions—Bipolar Version severity of mania –1.73 versus –1.05, P < 0.001 Response: 48.6% versus 22.2%, P = 0.002 Remission: 35.2% versus 11.1%, P = 0.001	Patient interviews, lab tests and Simpson-Angus Scale , the Barnes Akathisia Scale , and the Abnormal Involuntary Movement Scale
Tramontina 2009 Brazil	Aripiprazole vs.. Placebo Change in YMRS 27.22 vs. 19.52 P = 0.02 Response 88.9% vs. 52% Remission 72% vs. 32% P = 0.01 Change in SNAP-IV 0.79 vs. 0.55 P = 0.39	Checklist of 49 common aripiprazole AEs and open ended questions at visits

Evidence Table 23. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Tohen 2007 USA and Puerto Rico	Incidence of treatment-emergent adverse events frequency ≥5% significantly higher in the olanzapine group for appetite increase, weight increase, and somnolence and sedation items. Abnormal Involuntary Movement Scale (olanzapine, –0.10 [SD=0.71] versus placebo, 0.00 [SD=0.19], p=0.289), Simpson-Angus (olanzapine, 0.02 [SD=0.93] versus placebo,–0.02 [SD=0.14], p=0.769), Barnes scales (olanzapine, –0.04 [SD=0.44] versus placebo, 0.06 [SD=0.60], p=0.264)	41 withdrawal 4 due to AEs	
Tramontina 2009 Brazil	Aripiprazole vs. Placebo Incidence of AEs shown in graph	2 withdrawals 1 due to AEs	

Evidence Table 24. Quality assessment of randomized controlled trials in pediatrics with bipolar disorder

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Biederman 2005	NR	N/A	Yes	Yes	Open-label	Open-label	Open-label
DelBello 2002	Unclear, used random number generator	Unclear	Yes	Yes	Yes	Yes	Yes
Delbello 2009	Unclear, used random number generator	NR	Yes	Yes	Yes	Yes	Yes
Findling 2009	NR	NR	Unclear Missing data on some clinical chartactoristics. Reported data shows differences in age, % non-Hispanic/Latino, % without psychotic features,% without ADHD	Yes	NR (described as double-blind)	NR (described as double-blind)	Yes
Haas 2009	NR	NR	Yes	Yes	NR (described as double-blind)	NR (described as double-blind)	NR (described as double-blind)
Tohen 2007	NR	NR	Yes	Yes	NR (described as double-blind)	NR (described as double-blind)	NR (described as double-blind)
Tramontina 2009	Yes	Yes	Mostly: SES was significantly different, placebo group having more in the upper middle than aripiprazole	Yes	Yes	Yes	Yes

Evidence Table 24. Quality assessment of randomized controlled trials in pediatrics with bipolar disorder

Author, Year Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Maintenance of comparable groups	Intention-to-treat (ITT) analysis	Funding	Quality rating
Biederman 2005	Yes, No, No, No	Differential: Yes High: No	Unclear	Yes	Center grant from the Stanley Medical Research Institute	Fair
DelBello 2002	Yes, No, No, No	Differential: Yes High: No	Unclear	Yes	AstraZeneca	Fair
Delbello 2009	Yes, No, No, No	No/No	Yes	Yes	AstraZeneca Pharmaceuticals	Fair
Findling 2009	Yes, No, Yes, No	No/No	Yes	No	Otsuka Pharmaceutical Co., Ltd.	Fair
Haas 2009	Yes, No, Yes, No	No/No	Yes	No 169/170 included	Johnson & Johnson Pharmaceutical Research and Development, LLC.	Fair
Tohen 2007	Yes, No, No, No	79.4% compeleted olanzapine group 64.8% completed placebo group	Unclear	Yes	Eli Lilly & Co.	Fair
Tramontina 2009	Yes, No, No, No	No/No	Yes	Yes	Bristol-Myers Squibb	Good

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Alexopoulos 2008 USA Canada, France, the United Kingdom, and the United States	DB RCT (see run-in) subanalysis of older patients, 55 yrs or older 53 centers	Inclusion - 55 year or more with TRD (a history of resistance to standard antidepressant treatment, defined as failure to respond to at least one but no more than three antidepressants during the current episode, administered at adequate doses for a minimum of 6 consecutive weeks) HAM-D 17 or more and MMSE >23 Exclusion - dementia and all other DSM–IV axis 1 diagnoses, except generalized anxiety disorder and phobias, severe and unstable cardiovascular, kidney, liver, or eurological diseases.	Placebo or risperidone for maintenance	4-6 weeks citalopram, if no response augmentation with risperidone for 4-6 weeks, those in remission were randomized

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Alexopoulos 2008 USA Canada, France, the United Kingdom, and the United States	Yes for medical comorbidities	MADRS and HAM-D, time to relapse	Mean age 36.4 yrs 42% male	Placebo vs. risperidone HAM-D 7.2 vs. 7.9 MADRS 8.7 vs. 9.2	110/63/63

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow-up/analyzed	Results	Method of adverse events assessment
Alexopoulos 2008 USA Canada, France, the United Kingdom, and the United States	45/0/63	Placebo vs. risperidone Relapse in 180 days 65% vs. 56% Change in HAM-D 6.5 (7.5) vs. 8.3 (7.9) Change in MADRS 12.3 (11.4) vs. 9.8 (11.5)	Simpson-Angus Scale, Barnes Akathisia Scale, Abnormal Involuntary Movement Scale and reports of adverse events

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Alexopoulos 2008 USA Canada, France, the United Kingdom, and the United States	Placebo vs. risperidone Headache vs. 0 9.4 Insomnia 3.2 vs. 3.1 Diarrhea 6.5 vs. 0 Nausea 3.2 vs. 3.1 Somnolence 3.2 vs. 3.1 Dizziness 6.5 vs. 6.3 Dry mouth 6.5 vs. 3.1 URTI 6.5 vs. 6.3 Constipation 6.5 vs. 3.1 Fatigue 6.5 vs. 3.1 Weight increase 6.5 vs. 6.3 Pruritus 0 vs. 6.3 Fall 0 6.3 Lethargy 0 vs. 6.5 0 Seasonal allergy 6.5 vs. 0 Appetite increase 3.2 vs. 6.3 Dyspepsia 0 vs. 6.3 Joint stiffness 0 vs. 5.4 Peripheral swelling 0 vs. 6.3 Sensation of heaviness 0 vs. 6.3	45 withdrawals 4 due to AEs	Goes with - Rapaport MH, Gharabawi GM, Canuso CM, Mahmoud RA, et al: Effects of risperidone augmentation in patients with treatment resistant depression: results of open-label treatment followed by double-blind continuation. Neuropsychopharmacology 2006; 31: 2505–2513

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
AstraZeneca SAPPHIRE STUDY Study Code D1448CC00014 Year 2008 Argentina, Estonia, Finland, Russia, Ukraine, and the United States	DB RCT multicenter (53 centers)	Male or female patients, 66 years of age or older, with a documented clinical diagnosis meeting DSM-IV criteria of either 296.2x MDD, Single Episode, or 296.3x MDD, Recurrent. Diagnosis was to be confirmed by the MINI.The patients had to have a HAM-D total score ≥22 and HAM-D Item 1 score ≥2 at both enrollment and randomization to be eligible for the study.	Placebo vs Quetiapine XR 50-300 mg/day 9 week	Washout period of up to 28 days

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
AstraZeneca SAPPHIRE STUDY Study Code D1448CC00014 Year 2008 Argentina, Estonia, Finland, Russia, Ukraine, and the United States	NR	MADRS at each assessment week; HAM-D; CGI-S score; CGI-I score; Q-LES-Q; HAS; pain VAS Compared endpoint (week 9) and baseline	Mean age (SD): 71.3 (4.8) years 29.9% male 98.5% Caucasian 0.6% Black 0.9% Other	Placebo vs quetiapine DSM-IV diagnosis: n (%) ---296.2x MDD, Single Episode: 25 (14.6) vs 27 (16.5) ---296.3x MDD, Recurrent: 146 (85.4) vs 137 (83.5) Mean MADRS total score (SD): 28.2 (6.2) vs 27.5 (6.1) Mean HAM-D total score (SD): 25.2 (2.5) vs 25.4 (2.6) Mean HAM-D Item 1 (SD): 2.9 (0.6) vs 3.0 (0.6) Mean HAM-A total score (SD): 20.1 (5.3) vs 19.4 (5.6) Mean CGI-S total score (SD): 4.4 (0.6) vs 4.3 (0.5) Mean Q-LES-Q % maximum total score (SD): 41.9 (11.4) vs 44.1 (12.1)	NR/NR/338

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow- up/analyzed	Results	Method of adverse events assessment
AstraZeneca SAPPHIRE STUDY Study Code D1448CC00014 Year 2008 Argentina, Estonia, Finland, Russia, Ukraine, and the United States	80/NR/335	Placebo vs quetiapine Mean change in MADRS total score: -8.79 vs -16.33; *P≤0.001* Proportion with MADRS response (decrease in MADRS score of ≥50%): 30.41 vs 64.02; *P*≤0.001 Proportion with MADRS remission (total MADRS score ≤8): 17.0 vs 45.1; *P*≤0.001 Mean change in HAM-D total score: -8.62 vs -15.66; *P*≤0.001 Mean change in HAM-D Item 1: -1.13 vs -1.84; *P*≤0.001 Mean change in CGI-S total score: -0.77 vs -1.73; *P*≤0.001 Proportion improved on CGI-I: 39.18 vs 71.34; *P*≤0.001 Q-LES-Q % maximum total score: 9.17 vs 16.86; *P*≤0.001 Mean change in HAS total score: -5.20 vs -10.51; *P*≤0.001 Mean change in PSQI global score: -2.89 -6.42; *P*≤0.001 Mean change in Pain VAS: -9.01 vs -18.75; *P*≤0.001	Physical examination, laboratory values, vital signs, ECG, AEs, Treatment Discontinuation Signs and Symptoms scale, weight, BMI, waist circumference, SAR-S, BARS, AIMS, MADRS Item 10 score ≥4 or an AE of related to suicidality, and incidences of suicidality using Columbia-like analysis

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
AstraZeneca SAPPHIRE STUDY Study Code D1448CC00014 Year 2008 Argentina, Estonia, Finland, Russia, Ukraine, and the United States	Placebo vs quetiapine n (%) Death: 0 vs 0 Serious AEs: 2 (1.2) vs 4 (2.4) All AEs: 105 (61) vs 134 (80.7) Somnolence: 14 (8.1) vs 55 (33.1) Headache: 28 (16.3) vs 35 (21.1) Dry mouth: 18 (10.5) vs 34 (20.5) Dizziness: 26 (15.1) vs 32 (19.3) Fatigue: 7 (4.1) vs 13 (7.8) Insomnia: 10 (5.8) vs 13 (7.8) Constipation: 4 (2.3) vs 10 (6.0) Diarrhea: 12 (7.0) vs 9 (5.4) Nausea: 8 (4.7) vs 9 (5.4) Weight increased: 7 (4.1) vs 9 (5.4) Sedation: 2 (1.2) vs 8 (4.8) Asthenia: 1 (0.6) vs 6 (3.6) Extrapyramidal disorder: 1 (0.6) vs 6 (3.6) Abdominal pain upper: 4 (2.3) vs 5 (3.0) Back pain: 2 (1.2) vs 4 (2.4) Dysgeusia: 1 (0.6) vs 4 (2.4) Hypotension: 0 vs 4 (2.4) Pain in extremity: 2 (1.2) vs 4 (2.4) Hypertension: 4 (2.3) vs 2 (1.2) Nasopharyngitis: 6 (3.5) vs 2 (1.2) Tachycardia: 4 (2.3) vs 2 (1.2) Edema peripheral: 4 (2.3) vs 0 (0.0) AEs potentially related to EPS: 4 (2.3) vs 12 (7.2) Worsening SAR-S total scores: (8.1) vs 23 (14.1) Worsening AIMS total scores: 8 (4.7) vs 15 (9.2) Worsening BARS global scores: 2 (1.2) vs 2 (1.2)	Total Withdrawals: 80 Withdrawals due to AEs: 23	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
AstraZeneca OPAL STUDY Study Code D1448CC00003 Year 2008 United States	DB RCT Multicentre (35 sites)	Male and female patients, 18 to 65 years old inclusive, with clinical diagnosis using MINI and meeting DSM-IV of either 296.2x Major Depressive Disorder, Single Episode, or 296.3x Major Depressive Disorder, Recurrent; HAM-D score ≥22 and a HAM-D Item 1 (depressed mood) score ≥2 at both enrollment and randomization	Placebo vs quetiapine XR 150-300 mg/day 8 week	Washout period of up to 28 days

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
AstraZeneca OPAL STUDY Study Code D1448CC00003 Year 2008 United States	NR	MADRS at each assessment week, HAM-D, CGI-S, CGI-I, HAS, PSQI, Q-LES-Q, EuroQoL Health Utility Index Compared endpoint (week 8) and baseline	Mean age (SD): 42.9 (11.1) years 35.5% male 67.2% Caucasian 27.4% Black 1% Oriental 4.3 Other	Placebo vs Quetiapine DSM-IV diagnosis: n (%) ---296.2x MDD, Single Episode: 21 (13.8) vs 9 (6.1) ---296.3x MDD, Recurrent: 131 (86.2) vs 138 (93.9) Mean MADRS total score (SD): 29.3 (5.3) vs 29.7 (6.2) Mean HAM-D total score (SD): 25.6 (2.9) vs 25.4 (3.3) Mean HAM-D Item 1 (SD): 3.0 (0.5) vs 3.1 (0.5) Mean HAS total score (SD): 19.3 (5.7) vs 18.6 (5.4) Mean CGI-S total score (SD): 4.6 (0.7) vs 4.6 (0.7) Mean Q-LES-Q maximum total score (SD): 45.2 (15.1) vs 43.4 (15.0)	NR/NR/310

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow- up/analyzed	Results	Method of adverse events assessment
AstraZeneca OPAL STUDY Study Code D1448CC00003 Year 2008 United States	91/NR/299	Placebo vs Quetiapine Mean change in MADRS total score: -13.1 vs -16.49; *P*<0.01 Proportion with MADRS response (decrease in MADRS total score of ≥50%): 48.0% vs 61.9%; *P<0.05* Proportion with MADRS remission (total score ≤8): 25.0% vs 34.7%; *P*=0.052 Mean change in HAM-D total score: -12.35 vs -14.75; *P*<0.05 Mean change in HAM-D Item 1: -1.40 vs -1.71; *P<0.05* Mean change in CGI-S total score: -1.24 -1.64; *P*<0.01 Proportion improved on CGI-I: 52.0% vs 63.3%; *P*<0.05 Mean change in Q-LES-Q maximum total score: 11.93 vs 13.80 Mean change in HAS total score: -7.70 vs -9.14; *P*<0.05	Laboratory values, physical examination, vital signs, weight, waist circumference, CSFQ total score, ECG, SAR-S, BARS, AEs (including EPS-related), treatment discontinuation signs and symptoms, MADRS Item 10 (suicidal thoughts) score ≥4 or an AE related to suicidality, and incidences of suicidality using Columbia-like analysis

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
AstraZeneca OPAL STUDY Study Code D1448CC00003 Year 2008 United States	Placebo vs Quetiapine n (%) Death: 0 vs 0 Serious AEs: 2 (1.3) vs 3 (2.0) Any adverse event: 96 (61.9) vs 125 (82.2) Dry mouth: 10 (6.5) vs 51 (33.6) Sedation: 4 (2.6) vs 35 (23.0) Somnolence: 8 (5.2) vs 31 (20.4) Headache: 16 (10.3) vs 22 (14.5) Insomnia: 4 (2.6) vs 14 (9.2) Dizziness; 6 (3.9) vs 13 (8.6) Fatigue: 0 vs 11 (7.2) Nausea: 11 (7.1) vs 10 (6.6) Diarrhea: 6 (3.9) vs 10 (6.6) Increased appetite: 2 (1.3) vs 10 (6.6) Constipation: 2 (1.3) vs 9 (5.9) Nasal congestion: 3 (1.9) vs 9 (5.9) Arthralgia: 4 (2.6) vs 8 (5.3) Vomiting: 4 (2.6) vs 8 (5.3) Irritability: 2 (1.3) vs 6 (3.9) Upper respiratory tract infection: 6 (3.9) vs 6 (3.9) Gastroesophageal reflux disease: 0 vs 5 (3.3) Vision blurred: 0 vs 5 (3.3) Weight increased: 0 vs 5 (3.3) Abdominal pain upper: 0 vs 4 (2.6) Depression: 0 vs 4 (2.6) Dyspepsia: 2 (1.3) vs 4 (2.6) Nasopharyngitis: 11 (7.1) vs 4 (2.6) Rhinitis: 1 (0.6) vs 4 (2.6) Abdominal distension: 0 vs 3 (2.0) Akathisia: 0 vs 3 (2.0) Anxiety: 3 (1.9) vs 3 (2.0) Back pain: 2 (1.3) vs 3 (2.0) Extrapyramidal disorder: 1 (0.6) vs 3 (2.0) Joint stiffness: 0 vs 3 (2.0) Musculoskeletal stiffness: 2 (1.3) vs 3 (2.0) Muscle spasms: 1 (0.6) vs 3 (2.0) Myalgia: 1 (0.6) vs 3 (2.0) Sinusitis: 4 (2.6) vs 2 (1.3) Mean change in heart rate: +2.2 vs +5 beats per minute	Total Withdrawals: 91 Withdrawals due to AEs: 19	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
AstraZeneca Study Code D144CC00004 Year 2007 United States	DB RCT Multicentre (50 centers)	Male or female, 18 to 65 years of age, inclusive with a diagnosis of bipolar I disorder according to the DSM-IV text revision criteria of 296.4x (Bipolar I Disorder, Most Recent Episode Manic) or 296.6x (Bipolar I Disorder, Most Recent Episode Mixed) confirmed by the amended version of the SCID. Patients who experienced rapid cycling as defined in DSM-IV-TR were eligible to participate in the study. To be enrolled in the study, patients must have had at least 1 bipolar manic or mixed episode in the prior 5 years, a YMRS total score at screening of ≥20 with a score of ≥4 on 2 of 4 of the following core YMRS items: irritability, speech, content, and disruptive/aggressive behavior; and must have a Clinical Global Impression – Bipolar – Severity of Illness score of ≥4 on the overall bipolar illness item at randomization	Flexible doses QD Quetiapine XR (400 to 800 mg) or placebo 3 weeks	28-day washout period

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
AstraZeneca Study Code D144CC00004 Year 2007 United States	NR	YMRS total score, YMRS response (patients with ≥50% reduction of YMRS); YMRS remission (patients with a YMRS total score ≤12 at final visit); Clinical Global Impression - bipolar - severity; MADRS Compared endpoint to baseline.	Mean age: 41 years 60.1% male 47.1% Caucasian 47.7 Black/African American 1% American Indian/Alaskan Native 0.6% Asian 0.3% Native Hawaiian/ Pacific Islander 3.2% Other	Quetiapine vs Placebo YMRS (SD): 28.8 (5.4) vs 28.4 (5.1) MADRS (SD): 14.3 (7) vs 14.6 (6.4) Current episode, Manic: 57.7% vs 55.3% Current episode, Mixed: 42.3 vs 44.7% Median duration of present mania episode: 4 vs 4 weeks Those that attempted suicide: 56.4% vs 57.2%	NR/NR/316

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow- up/analyzed	Results	Method of adverse events assessment
AstraZeneca Study Code D144CC00004 Year 2007 United States	89/NR/308	Quetiapine vs Placebo Mean change in YMRS (SE): -14.34 (0.91) vs -10.52 (0.88); *P*<0.001 Responders: 55% vs 33.3%; *P*<0.001 Remission: 41.6% vs 27.7%; *P*0.006 Change in MADRS total score: Quetiapine was superior to placebo in decreasing depressive symptoms (*P*≤0.022)	Physical examinations, laboratory values (including glucose/lipids), vital signs, electrocardiogram (ECG) AEs, including somnolence, EPS including akathisia, diabetes mellitus, QT prolongation, neutropenia/agranulocytosis, and suicidality; Serious adverse events (SAEs) SAR-S, BARS Incidence of treatment-emergent depression (AE of depression or depressed mood, and or MADRS scores ≥18 on 2 consecutive assessments or on the final assessment); Change in weight from baseline (randomization [Visit 2]) to final visit (Visit 6) Incidences of suicidality using a suicidality classification similar to the one established by Columbia University

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
AstraZeneca Study Code D144CC00004 Year 2007 United States	Quetiapine vs Placebo Death: 0 vs 1 (0.6%) Patients with any AE: 128 (84.8%) vs 107 (66.9%) Sedation: 34.4% vs 7.5% Dry mouth: 33.8% vs 6.9% Somnolence: 16.6% vs 4.4% AEs potentially related to EPS: 6.6% vs 3.8% Treatment-emergent depression (criterion of MADRS): 0 vs 1 (0.6%) Suicidal behavior/ideation: 1.3% vs 3.1% Weight change: +1.3 vs +0.1 kg Increases in weight ≥7%: 5.1% vs 0%	Total Withdrawals: 89 Withdrawals due to AEs: 20	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
AstraZeneca AMETHYST STUDY Study Code D1448CC00005 Year 2008 North America, Europe, South Africa	DB RCT Multicenter (237 sites)	Male or female patients 18 to 65 years old, with a documented clinical diagnosis of MDD together with an acute depressed episode confirmed by Mini-International Neuropsychiatric Interview and meeting the DSM-IV Text Revision of either Criteria 296.2x MDD, Single Episode or Criteria 296.3x MDD, Recurrent; have had a current episode of depression that was at least 4 weeks and less than 12 months in duration prior to enrollment; have had a Hamilton Rating Scale for Depression (HAM-D) total score of ≥20 and a HAM-D item 1 score of ≥2 at enrollment. For inclusion in the open-label stabilization and randomized treatment phases, the patient had to have a MADRS score ≤12 and a CGI-S score ≤3.	Placebo vs Quetiapine XR 50-300 mg/day 52 weeks	Quetiapine open-label run-in period of 4 to 8 weeks, an open-label stabilization treatment period of at least 12 weeks

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
AstraZeneca AMETHYST STUDY Study Code D1448CC00005 Year 2008 North America, Europe, South Africa	NR	Time from randomization to occurrence of a depressed event (A depressed event was defined as fulfilling at least 1 of the following: (a) Initiation of pharmacological treatment by the Investigator, other than the allowed hypnotics, to treat Clinical Study Report Synopsis depressive symptoms, (b) Initiation of pharmacological treatment by the patient for at least 1 week, other than the allowed hypnotics, to treat depressive symptoms, (c) Hospitalization for depressive symptoms, (d) MADRS score ≥18 at 2 consecutive assessments 1 week apart or at the final assessment if the patient discontinued, (e) CGI-S score ≥5, or (f) Suicide attempt or discontinuation from study due to imminent risk of suicide) HAS, MADRS, Q-LES-Q, PSQI global socre, Sheehan Disability Scale	Mean age: 44 years 34% male 87.5% Caucasian 9.1% Black 0.6% Oriental 2.7% Other	Placebo vs Quetiapine DSM-IV TR diagnosis: n (%) ---296.2x MDD, single episode: 64 (16.7) vs 51 (13.2) ---296.3x MDD, recurrent: 320 (83.3) vs 336 (86.8) Mean MADRS (SD): 27.7 (5.8) vs 28.59 (5.9) Mean HAM-D (SD): 24.0 (3.1) vs 24.1 (3.2) Mean CGI-S (SD): 4.4 (0.7) vs 4.49 (0.8)	NR/NR/1876 enrolled (open-label); 776 randomized (double-blind)

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow- up/analyzed	Results	Method of adverse events assessment
AstraZeneca AMETHYST STUDY Study Code D1448CC00005 Year 2008 North America, Europe, South Africa	NR/NR/771	Placebo vs Quetiapine Time to depression relapse: (presented graphically) Number of relapses n (%): 132 (34.4%) vs 55 (14.2%); *P*<0.001 Mean change in MADRS total score (SE): 2.03 (0.21) vs 0.15 (0.20); *P*<0.001 Mean change in CGI-S score (SE): 0.23 (0.04) vs -0.03 (0.03); *P*<0.001 Mean change in HAS total scorec (SE): 1.58 (0.18) vs 0.20 (0.17); *P*<0.001 Mean change in HAS psychic anxiety factors score (SE): 1.23 (0.12) vs 0.16 (0.11); *P*<0.001 Mean change in HAS somatic anxiety factors score: 0.33 (0.09) vs 0.06 (0.09); *P*=0.031 Mean change in Q-LES-Q percentage of the maximum total score (SE): -0.36 (0.65) vs 0.52 (0.59); *P*=0.303 Mean change in Q-LES-Q Item 15 (SE): -0.24 (0.04) vs -0.13 (0.04); *P*=0.039 Mean change in Q-LES-Q Item 16 (SE): -0.12 (0.04) vs 0.02 (0.03); *P*=0.004 Mean change in PSQI global score (SE): 1.35 (0.17) vs 0.06 (0.15); *P*<0.001	Laboratory values, physical examination, vital signs, weight, BMI, waist circumference, ECG, SAR-S, BARS, AIMS, AEs (including EPS-related), Treatment Discontinuation Signs and Symptoms MADRS Item 10 score ≥4 or an AE related to suicidality.

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
AstraZeneca AMETHYST STUDY Study Code D1448CC00005 Year 2008 North America, Europe, South Africa	Placebo vs Quetiapine n (%) Death: 1 (0.3) vs 0 Serious AEs: 8 (2.1) vs 8 (2.0) Any AEs: 233 (60.5) vs 246 (62.9) Weight increased: 6 (1.6) vs 38 (9.7) Nasopharyngitis: 25 (6.5) vs 28 (7.2) Headache: 44 (11.4) vs 27 (6.9) Dizziness: 17 (4.4) 26 (6.6) Insomnia: 57 (14.8) vs 22 (5.6) Diarrhea:26 (6.8) vs 21 (5.4) Arthralgia: 9 (2.3) vs 19 (4.9) Fatigue: 10 (2.6) vs17 (4.3) Back pain: 10 (2.6) vs 15 (3.8) Somnolence: 0 vs 15 (3.8) Upper respiratory tract infection: 16 (4.2) vs 15 (3.8) Dry mouth: 6 (1.6) vs 14 (3.6) Nausea: 38 (9.9) vs 14 (3.6) Sinusitis: 9 (2.3) vs 12 (3.1) Sedation: 1 (0.3) vs 10 (2.6) Blood pressure increased: 2 (0.5) vs 9 (2.3) Myalgia: 5 (1.3) vs 9 (2.3) Urinary tract infection: 4 (1.0) vs 9 (2.3) Constipation: 1 (0.3) vs 8 (2.0) Musculoskeletal pain: 5 (1.3) vs 8 (2.0) Vomiting: 9 (2.3) vs 8 (2.0) Pain in extremity: 8 (2.1) vs 6 (1.5) Anxiety: 10 (2.6) vs 5 (1.3) Irritability: 12 (3.1) vs 3 (0.8) No mean change in total SAR-S, BARS or AIMS was observed for either group.	Total Withdrawals: NR Withdrawals due to AEs: 45	During the open-label phase of the study, the incidence of any AE was 85.4% and the proportion of patients having AEs leading to discontinuation was 19.8%. The incidence of SAEs, including deaths was 2.1% and a total of 3 deaths (metastatic neoplasm, myocardial infarction, and death [cause not documented in clinical database] were reported during the open-label phase.

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
AstraZeneca Pearl Study Study Code D1448CC00006 Year 2007 USA	DB RCT Multicenter (56 centers)	Male or female patients, 18 to 65 years old, inclusive, with DSM-IV diagnosis of MDD, Single Episode (296.2x) or MDD, Recurrent (296.3x) as confirmed by MINI. Patients should have been on treatment with 1 of the following antidepressants for at least 6 weeks prior to enrollment (at least minimum effective antidepressant dose according to the prescribing information), with at least 1 dose increase when permitted according to the prescribing information: amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine. In addition, patients had to have a HAM-D total score ≥20 and a HAM-D Item 1 (depressed mood) score ≥2 at both enrollment and randomization.	Placebo vs quetiapine XR 150 mg/day vs quetiapine XR 300 mg/kg 6 weeks	Washout period of up to 14 days of all prohibited medications

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
AstraZeneca Pearl Study Study Code D1448CC00006 Year 2007 USA	Ongoing antidepressant treatment	MADRS at each assessment week; HAM-D; CGI-S score; CGI-I score; Q-LES-Q; PSQI; HAS. Compared endpoint (week 6) and baseline	Mean age (SD): 45.4 (11.1) 27.5% male 90% Caucasian 8.1% Black 0.2% Oriental 1.6% Other	Placebo vs Quetiapine 150 mg/kg vs Quetiapine 300 mg/kg DSM-IV diagnosis: n (%) ---296.2x MDD, Single Episode: 10 (7.0) vs 8 (5.6) vs 14 (9.6) ---296.3x MDD, Recurrent: 133 (93.0) vs 135 (94.4) vs 132 (90.4) Mean MADRS total score (SD): 27.6 (5.5) vs 27.2 (5.2) vs 27.6 (5.0) Mean HAM-D total score (SD): 24.2 (3.1) vs 24.0 (3.4) vs 24.0 (2.9) Mean HAM-D Item 1 score (SD): 2.9 (0.6) vs 2.9 (0.6) vs 2.9 (0.6) Mean HAM-A total score (SD): 17.9 (5.6) vs 17.7 (5.7) vs 18.7 (5.5) Mean CGI-S score (SD): 4.4 (0.7) vs 4.4 (0.6) vs 4.5 (0.7) Mean Q-LES-Q percent maximum total score (SD): 45.2 (13.6) vs 44.3 (13.8) vs 47.9 (14.8)	NR/NR/446

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow- up/analyzed	Results	Method of adverse events assessment
AstraZeneca Pearl Study Study Code D1448CC00006 Year 2007 USA	102/NR/432	Placebo vs Quetiapine 150 mg/kg vs Quetiapine 300 mg/kg; *P* value is versus placebo. Mean change in MADRS total score: -11.70 vs -13.60 vs -14.70 (*P*<0.01) Proportion with ≥50% MADRS response: 46.2% vs 51.7% vs 58.9% (*P*<0.05) Proportion with MADRS remission (total score ≤8): 24.5% vs 35.0% vs 42.5% (*P*<0.01) Mean change in HAM-D total score: -10.80 vs -12.63 (*P*<0.05) vs -13.53 (*P*<0.01) Mean change in HAM-D Item 1 score: -1.35 vs -1.53 vs -1.60 Mean change in HAS total score: -6.67 vs -7.43 vs -8.50 (*P*<0.05) Mean change in CGI-S score: -1.23 vs -1.47 vs -1.52 (*P*<0.05) Proportion improved on CGI-I: 46.9% vs 58.0% vs 58.2% (*P*<0.05) Mean change in Q-LES-Q percent maximum total score: 11.32 vs 10.37 vs 11.82	Laboratory values, physical examination, vital signs, weight, BMI, waist circumference, ECG, SAR-S total score, BARS global assessment (Item 4) score, CSFQ total score, AEs (including EPS-related), Treatment Discontinuation Signs and Symptoms; MADRS Item 10 (suicidal thoughts) score ≥4 or an AE of or related to suicidality, and suicidality analysis.

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
AstraZeneca Pearl Study Study Code D1448CC00006 Year 2007 USA	Placebo vs Quetiapine 150 mg/kg vs Quetiapine 300 mg/kg n (%) Death: 0 vs 0 vs 0 Serious AEs: 1 (0.7) vs 1 (0.7) vs 0 Any AEs: 99 (66.9) vs 122 (82.4) vs 130 (87.2) Dry mouth: 13 (8.8) vs 52 (35.1) vs 66 (44.3) Somnolence: 6 (4.1) vs 43 (29.1) vs 43 (28.9) Sedation: 6 (4.1) vs 25 (16.9) vs 33 (22.1) Dizziness: 8 (5.4) vs 17 (11.5) vs 21 (14.1) Constipation: 5 (3.4) vs 11 (7.4) vs 16 (10.7) Nausea: 12 (8.1) vs 13 (8.8) vs 15 (10.1) Insomnia: 10 (6.8) vs 16 (10.8) vs 12 (8.1) Headache: 20 (13.5) vs 21 (14.2) vs 11 (7.4) Fatigue: 7 (4.7) vs 23 (15.5) vs 10 (6.7) Diarrhea: 10 (6.8) vs 10 (6.8) vs 10 (6.7) Increased appetite: 8 (5.4) vs 8 (5.4) vs 10 (6.7) Weight increased: 1 (0.7) vs 3 (2.0) vs 9 (6.0) Upper respiratory tract infection: 5 (3.4) vs 7 (4.7) vs 6 (4.0) Back pain: 0 vs 3 (2.0) vs 6 (4.0) Irritability: 9 (6.1) vs 9 (6.1) vs 5 (3.4) EPS-related AEs: 5 (3.4) vs 5 (3.4) vs 12 (8.1) Weight gain ≥7%: (1-2) vs (1-2) vs (8)	Total Withdrawals: 102 Withdrawals due to AEs: 48	1 Placebo patient had an onset of AE (ECG abnormalities) prior to randomization, and was discontinued due to this AE during the randomized treatment period.

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Bauer 2009 Multinational	DB RCT Multicenter	Inclusion - Male or female; 18 to 65 years old; MDD, single or recurrent; HAM-D 17 20 or more with item 1 (depressed mo0od) 2 or more and a history of inadequate response Exclusion- another Axis 1 diagnosis; Axis 2 that impacts patient's current diagnosis; current duration 12 months or more or less than 4 weeks; substance abuse or dependence; clinically significant illness: suicide ideation	Adjunctive treatment with quetiapine 150 or 300 or placebo	14 day washout
Berman 2007 USA	DB RCT Multicenter (24)	Patients 18 to 65 yrs; met DSMIV criteria for a major depressive episode lasting ≥8 weeks; inadequate response to a previous antidepressant as defined by <50% reduction in severity of depressive symptoms—of at least 6 weeks duration.	adjunctive placebo or aripiprazole (2–20 mg/day; maximum 15 mg/day in patients receiving fluoxetine or paroxetine. Mean dose aripiprazole 11.8 mg/day during last week of DB phase.	7-28 day screening period, 781 patients single-blind adjunctive placebo plus open-label antidepressant for 8 weeks to confirm inadequate response to antidepressants; 362 patients with inadequate response were randomized to 6 week DB treatment phase.

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Bauer 2009 Multinational	Benzodiazepines and anticholinergics	MADRS, HAM-D, HAM-A, CGI-S, Q-LES-Q, Pittsburgh Sleep Quality Index assessed at baseline and study visits at weeks 1,2,4 and 6 and CGI-I at end	Mean age 48.7 yrs 37.4% male 98% white	19% single episode 81% recurrent	572/510/493
Berman 2007 USA	NR	MADRS, Sheehan Disability Scale (SDS), Inventory of Depressive Symptomatology Self-Report Scale (IDS-SR), CGI-S, CGI-I	Mean age 45 y 37% male 90% White 7% Black 0.8% Asian 2.2% Other	Single episode 26% Recurrent 74%	1044/781/362

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow-up/analyzed	Results	Method of adverse events assessment
Bauer 2009 Multinational	69/3/493	Placebo vs. Quet150 vs. Quet300 Change in MADRS -12.21 vs -15.26 vs -14.94 MADRS response 46.3% vs 55.4% vs 57.8% (vs. placebo P < 0.05) Remission 23.8% vs 36.1% (vs. placebo P < 0.05) vs 31.1% Change in HAM-D -11.3 vs. -13.81 vs. -13.56 CGI-S -1.25 vs. -1.72 vs. -1.64 (both vs. placebo P < 0.01) CGI-! of 1 or 2 52.5% vs. 64.5% (vs. placebo P < 0.05) vs. 62.7%	Self-reported, lab tests and BAS, SA and CSFQ (Changes in Sexual Functioning Questionnaire)
Berman 2007 USA	33/9/320	Placebo (N=178) vs. aripiprazole (N=184) at 6 weeks: MADRS remission 15.7% vs. 26.0%; P=0.011 MADRS response 23.8% vs. 33.7%; P=0.027 MADRS mean change –5.8 vs. -8.8; P<.001 SDS mean change –0.65 vs. –1.1; P=ns CGI-I, mean (SE): 2.81 (0.09) vs. 2.49 (0.08); P=0.003 IDS-SR change, mean (SE): –5.2 (0.8) vs. –7.0 (0.8); P=0.076 CGI-S change, mean (SE): –0.64 (0.08) vs. –1.03 (0.08); P < 0.001	Clinician monitoring adverse events (AEs), body weight, vital signs, laboratory parameters, 12- lead electrocardiogram, and evaluation of extrapyramidal symptoms using the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale, and Barnes Akathisia Clinical Assessment (BARS).

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Bauer 2009 Multinational	Placebo vs. Quet150 vs. Quet300Dry mouth 6.8 vs. 20.4 vs. 35.6 Somnolence 3.1 vs. 16.8 vs. 23.3 Fatigue 3.1 vs. 13.2 vs. 14.7 Sedation 4.3 vs. 9.6 vs. 12.9 Constipation 3.7 vs. 4.2 vs. 10.4 Dizziness 7.5 vs. 11.4 vs. 9.2 Headache 9.9 vs. 9.0 vs. 8.0 Nausea6.2 vs. 5.4 vs, 5.5 Nasopharyngitis6.2 vs. 3.0 vs. 3.1	69 withdrawals 35 due to AEs	
Berman 2007 USA	Placebo (N=176) vs. aripiprazole (N=182), N (%): Akathisia 8 (4.5) vs. 42 (23.1) Restlessness 6 (3.4) vs. 26 (14.3) Upper respiratory tract infection 7 (4.0) vs. 15 (8.2) Insomnia 4 (2.3) vs. 14 (7.7) Vision blurred 3 (1.7) vs. 12 (6.6) Fatigue 6 (3.4) vs. 11 (6.0) Headache 19 (10.8) vs. 11 (6.0) Diarrhea 10 (5.7) vs. 6 (3.3) Dry mouth 11 (6.3) vs. 6 (3.3) Nausea 9 (5.1) vs. 5 (2.7)	33 withdrawals 10 due to AEs (6 aripiprazole, 4 placebo)	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Berman 2009 USA	DB RCT Multicenter (36)	Patients 18 to 6 5 yrs; met DSMIV criteria for a major depressive episode lasting ≥8 weeks; inadequate response to a previous antidepressant as defined by <50% reduction in severity of depressive symptoms—of at least 6 weeks duration.	adjunctive placebo or aripiprazole (2–20 mg/day; maximum 15 mg/day in patients receiving fluoxetine or paroxetine	7-28 day screening period, 827 patients single-blind adjunctive placebo plus open-label antidepressant for 8 weeks to confirm inadequate response to antidepressants; 349 patients with inadequate response were randomized
Chaput 2008 Canada	DB RCT Single center (though not explicitly stated)	Inclusion - TRD (Treatment refractoriness was determined by the failure of 2 (or more) 8-week treatments with 2 different classes of antidepressants. In addition, for at least 3 of these eight weeks, doses were required to be at or near the highest therapeutically recommended doses), with HAM-D 20 or more and CGI-S of 4 or more.. Exclusion - a current risk of suicide, women of childbearing potential who were pregnant (or planning pregnancy), breast-feeding or not using medically adequate means of birth control; a DSM-IV diagnosis of bipolar disorder, schizophrenia, personality disorder (borderline, antisocial, schizoid, schizotypal or paranoid), panic, generalized anxiety, obsessive-compulsive, somatoform or organic mental disorder, anorexia nervosa, bulimia or those with definite or suspected substance abuse; requiring concurrent treatment with any psychotropic medication or those with serious or unstable medical illnesses, known psychotropic drug allergies or co-existing diseases or treatments that might contraindicate the use of the study drug	Quetiapine (mean dose 147.7 mg/day) or placebo as an adjunct to their 12 weekly CBT sessions	Open period of lithium augmentation of three weeks, those that did not respond were randomized after 8 days of being tapered off

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Berman 2009 USA	Benzotropine or propranolol	MADRS, Sheehan Disability Scale (SDS), HAM-D, CGI-S, Q-LES-Q	45 yrs 27% male 87% White 9% Black 1% Asian 3% Other	13% single episode	1147/NR/847
Chaput 2008 Canada	zopiclone or temazepam as hypnotics on a PRN basis	HAM-D, MADRS, CGI-S and CGI-I) were performed at baseline and weeks 3 and 4 and at every two weeks thereafter. The EPS scale, the BAS, the HADS and Q-LES-Q were repeated at week 16 or at LOCF following randomization.	Mean age 43.7 years 26% male Ethnicity NR	Mean HAM-D 23 Mean MADRS 30.7 Mean CGI-S 4.2	40/34/31 40 initial screen, 31 entered open label lithium, 5 responded, 22 entered DB RCT

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow-up/analyzed	Results	Method of adverse events assessment
Berman 2009 USA	53/5/349	Placebo vs. aripiprazole at 6 weeks 914 weeks total) MADRS remission 18.9% vs. 36.8% MADRS response 26.6% vs. 56.6% Mean change in MADRS –6.4 vs. -10.1; P<.001; treatment difference –3.7; 95% CI −5.4, –2.0 SDS –0.8 (0.2) vs. –1.2 (0.2) P= 0 .08 CGI-I 2.8 (0.1) vs. 2.4 (0.1) P = 0.001 Change in HAM-D –5.1 (0.6) vs. –7.6 (0.6) P < 0.001 CGI-S change –0.7 (0.1) vs. –1.1 (0.1) P < 0.001 Q-LES-Q general subscore 5.2 (1.4) vs. 9.8 (1.4) P = 0 .004	Clinician monitoring adverse events (AEs), body weight, vital signs, laboratory parameters, 12- lead electrocardiogram, and evaluation of extrapyramidal symptoms using the Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale, and Barnes Akathisia Clinical Assessment (BARS)
Chaput 2008 Canada	7/0/22	Quetiapine vs. placebo HAM-D P < 0.05 HADS 20% vs. 6% ns CGI-S 33% vs. 12% P = ns CGI-I 33%c 23% P = ns Q-LES-Q 29% vs. 2% P < 0.05d	EPS, BAS, lab tests and self report

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Berman 2009 USA	Placebo vs. aripiprazole n(%) Akathisia 6 (3.5) vs.32 (18.2) Headache 14 (8.1) vs. 15 (8.5) Somnolence 1 (0.6) vs. 10 (5.7) Dizziness 5 (2.9) vs. 9 (5.1) Restlessness 6 (3.5) vs. 22 (12.5) Insomnia 9 (5.2) vs. 15 (8.5) Constipation 6 (3.5) vs. 10 (5.7) Diarrhea 13 (7.6) vs. 10 (5.7) Nausea 10 (5.8) vs. 7 (4.0) Upper respiratory tract infection 13 (7.6) vs. 13 (7.4) Fatigue 8 (4.7) vs. 16 (9.1) Vision blurred 3 (1.7) vs. 13 (7.4) Suicidal ideation 0 vs. 1 (0.6) Arterial occlusive disease 1 (0.6) vs. 0	53 withdrawals 14 due to AEs (11 aripiprazole, 3 placebo)	
Chaput 2008 Canada	Quetiapine vs. placebo somnolence 7 vs. 1, P < 0.01 insomnia 5 vs. 2 headache 4 vs 1 dry mouth 4 vs. 1 nausea 2 vs. 2 gastrointestinal discomfort 2 vs. 3 labile hypertension 1 vs. 1	7 withdrawals due to AES NR (1 possible?)	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Corya 2006 16 countries	DB RCT Multicentre (90 sites)	Inclusion: at least 18 years of age, had a CGI severity score of 4 or greater, and met criteria for DMS-IV diagnosis of major depressive disorder, single episode or recurrent, without psychotic features; documented history of a failure to achieve a satisfactory response to a selective serotonin reuptake inhibitor antidepressant after at least 6 weeks of therapy at a therapeutic dose (i.e., citalopram 40 mg/day, fluoxetine 40 mg/day, paroxetine 40 mg/day, or sertraline 150 mg/day Exclusion: current or past diagnosis of schizophrenia, schizoaffective disorder, other psychotic disorders, bipolar I disorder, bipolar II disorder, posttraumatic stress disorder, major depressive disorder with seasonal pattern, or dissociative disorders (as defined in DSM-IV); female patients who were pregnant or nursing	Olanzapine and fluoxetine 1/5 or 6/25 or 6/50 or 12/25 or 12/50 mg/day Olanzapine (6 or 12 mg/day) Fluoxetine (25 or 50 mg/day) Venlafaxine 75-375 mg/day Treated for 12 weeks after taper phase	2 to 7 day screening phase 7 week open-label lead-in phase with venlafaxine 75-375 mg/day and patients with less than 30% improvement in MADRS total score proceeded to next phase 5 to 9 day double-blind taper phase

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Corya 2006 16 countries	Concomitant medications with primary central nervous system activity were not allowed, with the exception of benzodiazepines as permitted at doses up to an equivalent of 4 mg of lorazepam per day.	MADRS, CGI-depression, HAS, Brief Psychiatric Rating Scale Efficacy scales were administered at baseline and at all acute phase visits (except for the Brief Psychiatric Rating Scale which was administered at baseline, at 6 weeks, and at end point)	Mean age (SD): 45.7 (10.8) years 72.5% female 89.9% Caucasian	Median length of current episode: 186 days MADRS score (SD): 30 (6.8) HAS score (SD): 17.5 (6.6) CGI-Depression (SD): 4.4 (0.8) Brief Psychiatric Rating Scale (SD): 16 (6.4)	NR/807/483

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow- up/analyzed	Results	Method of adverse events assessment
Corya 2006 16 countries	118/10/483	OFC (Olanzapine/Fluoxetine - combined 4 highest dosing arms) vs Olanzapine vs Fluoxetine vs Venlafaxine vs Olanzapine/Fluoxetine 1/5 (low dose) (*P* comparisons for Olanzapine/Fluoxetine high dose arms vs the 3 other groups only) Mean change in MADRS (SE): -14.06 (0.59) vs -7.71 (1.17); *P*<0.001 vs -11.7 (1.14) vs -13.73 (1.16) vs -11.97 (1.13) Mean change in CGI-Depression (SE): -1.51 (0.07) vs -0.91 (0.15); *P*<0.001 vs -1.26 (0.15) vs -1.49 (0.14) vs -1.23 (0.14) Mean change in HAS (SE): -7.43 (0.43) vs -4.86 (1.01) vs -5.3 (1.01); *P*=0.039 vs -5.89 (0.94) vs -6.33 (0.87) Mean change in brief Psychiatric Rating Scale (SE): -6.01 (0.4) vs -3.16 (1.04) vs -4.82 (0.88) vs -4.76 (0.98) vs -4.46 (1.07)	Safey monitoring included complete physical examinations, medical history, ECG, laboratory analyses, EPS: Simpson-Angus Scale, AIMS, Barnes Akathisia Scale. Adverse events were recorded at each visit. EPS scales administered at baseline and at all acute phase visits (except for the HAS which was administered at baseline, at 6 weeks, and at end point)

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Corya 2006 16 countries	OFC (Olanzapine/Fluoxetine - combined 4 highest dosing arms) vs Olanzapine vs Fluoxetine vs Venlafaxine vs Olanzapine/Fluoxetine 1/5 (low dose) Weight gain: 25% vs 26% vs 13% vs 5% vs 19% Somnolence: 22% vs 18% vs 5% vs 8% vs 8% Increased appetite: 16% vs 16% vs 7% vs 5% vs 14% Dizziness: 14% vs 10% vs 10% vs 5% vs 22% Dry mouth: 13% vs 16% vs 7% vs 5% vs 7% Asthenia: 12% vs 18% vs 8% vs 8% vs 8% Peripheral edema: 11% vs 8% vs 0 vs 2% vs 5% Headache: 10% vs 10% vs 17% vs 17% vs 24% No significant increases in measures of extrapyramidal symtpoms in patients treated with OFC No significant group differences on vital signs. No statistically significant differences in nonfasting blood glucose. Small increases in corrected QT interval for OFC (5.7 ms; SD, 18.5) similar to fluoxetine (5.9 ms; SD, 15.8)	Total withdrawals: 118 Withdrawals due to AEs: 40	OFC includes the four highest dosing arms of olanzapine/fluoxetine . One death in the OFC group.

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Cutler 2009 USA	DB RCT Multicenter	Inclusion - male or female outpatients, 18-65 yrs, HAM-D 22 or more, HAM-D item 1 (depressed) 2 or more Exclusion - another DSM-I diagnosis, psychosis, Axis II disorder that would impact psychiatric state, , episode less than 4 weeks or more than 12 months, clinically significant comorbidity, suicide or homicide risk.	Quetiapine (150 or 300 mg) vs. placebo vs. duloxetine (60 mg)	7 to 28 day wash out and enrollment period

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Cutler 2009 USA	Non-psychotropic medications, contraceptives or OTCs, lorazepam, zolpidem, zalephon, zopiclone, chloral hydrate, anticholinergics	MADRS, HAM-D, CGI-S, HAM-A, PSQI, at baseline, weeks 1,2,4,6	Mean 41.3 years 40% male 74% White 21% Black 1% Asian 4% Other	12% single episode 88% recurrent	912/NR/ 612

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow-up/analyzed	Results	Method of adverse events assessment
Cutler 2009 USA	170/32/587	Placebo vs. Q150 vs. Q300 vs. Duloxetine Change in MADRS -11.18 vs. -14.81** vs. -15.29** vs. -14.64 * Responders 36.2% vs. 54.4%* vs. 55.1%* vs. 49.6%*** Remission 20.4% vs. 26.5% vs. 32.0%*** vs. 31.9%*** Change in HAM-D -10.6 vs. -13.12* vs. -14.02** vs. -12.37*** Change in HAM-A -5.55 vs. -7.76* vs. -7.38* vs. -7.83* Change in CGI-S -1.06 vs. 1.43* vs. -1.6** vs. -1.53** PSQI -2.95 vs. -4.59** vs. -4.93** vs. -3.24 *** P < 0.05 vs. placebo * P < 0.01 vs. placebo ** P < 0.001 vs. placebo	Patient reported, clinician assessed using MedDRA

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Cutler 2009 USA	Placebo vs. Q150 vs. Q300 vs. Duloxetine (%) Dry mouth 8.9 vs. 33.6 vs.38.2 vs. 18.8 Sedation 5.1 vs 38.8 vs. 36.8 vs. 16.1 Somnolence 7.0 vs. 24.3 vs. 27.0 vs. 12.8 Dizziness 10.8 vs. 14.5 vs. 19.1 vs. 16.8 Headache 10.2 vs. 10.5 vs. 9.2 vs. 18.1 Constipation 6.4 vs. 5.9 vs. 8.6 vs. 11.4 Irritability 4.5 vs. 1.3 vs. 5.9 vs. 0 Dyspepsia 3.2 vs. 3.9 vs. 5.3 vs. 5.4 Fatigue 0 vs. 2.6 vs. 5.3 vs. 6.7 Nausea 9.6 vs. 10.5 vs. 5.3 vs. 36.2 Vision blurred 1.9 vs. 5.3 vs. 5.3 vs. 2.7 Increased appetite 1.9 vs. 5.9 vs. 3.9 vs 2.0 Diarrhea 6.4 vs. 4.6 vs. 2.6 vs. 4.0 URTI 7.0 vs. 2.0 vs. 2.6 vs. 4.0 Abnormal dreams 0.6 vs. 6.6 vs. 2.0 vs. 2.7 Pollakiuria 1.3 vs. 3.3 vs. 2.0 vs. 5.4 Insomnia 7.0 vs. 1.3 vs. 1.3 vs. 14.8 Decreased appetite 0.6 vs. 3.3 vs. 0 vs. 5.4 Hyperhidrosis 0.6 vs. 0 vs. 0 vs. 7.4 AEs related to EPS 3.2 vs. 4.6 vs. 5.3 vs. 8.1	170 withdrawals 80 due to AEs	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Dunner 2007 USA	Open label 6 week lead-in, 6 week DB RCT Multicenter	Inclusion - Adult outpatients, 21 to 65 years old, at least one course treatment for 4 weeks with no response on clinically appropriate anti-depressant and MADRS of 20 or more Exclusion - DSM-IV diagnosis of psychosis, PTSD, panic disorder, OCD; substance abuse or dependence; treatment with antipsychotic; fluoxetine or ECT in last 6 weeks; abnormal ECG medications known to prolong QTc interval; any acute or unstable medical illness; pregnant or breastfeeding	3 groups - sertraline 100 to 200 mg/day plus placebo or plus ziprasidone 80 mg/day, or plus ziprasidone 160 mg/day	! Week lead-in then 6 weeks monotherapy

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Dunner 2007 USA	NR	MADRS, HAM-D, CGI-S, CGI-I, HAM-A, baseline and endpoint	Mean age 44 years 50% male 89% white	64% had failed to respond to at least 2 classes of Ads	90/64/64

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow-up/analyzed	Results	Method of adverse events assessment
Dunner 2007 USA	26 (Placebo 5, Zip80 11, Zip160 10) /0/64	Ziprasidone 80 mg/day vs. ziprasidone 160 mg/day vs. placebo Change in MADRS -5.98 +/- 1.87 vs. -8.27 +/- 2.17 vs. -4.45 +/- 2.03 (P = NS). Response 19% (N = 4) vs. 32% (N = 6) vs. 10% (N = 2) (P = NS). Change in HAM-D -3.39 (1.36) vs -5.04 (1.54) vs -2.48 (1.47) Change in CGI-S -0.46 (0.25) vs -1.01 (0.29) vs -0.1 (0.28) Change in CGI-I -0.39 (0.27) vs -0.63 (0.32) vs -0.21 (0.30) Change in HAM-A -1.11 (1.46) vs -2.54 (1.61) vs -1.06 (1.52)	Vital signs, lab tests, physical exams, SAS, BAS and AIMS

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Dunner 2007 USA	Ziprasidone 80 mg/day vs. ziprasidone 160 mg/day vs. placebo % one or more AEs 100% vs. 84.2% vs. 40% Insomnia 36.4 vs. 31.6 vs. 5 Asthenia 22.7 vs. 26.3 vs. 0 Agitation 22.7 vs 26.3 vs 0 Somnolence 22.7 vs. 15.8 vs. 10 Dizziness 18.2 vs. 21.1 vs. 0 Tremor 22.7 vs. 10.5 vs. 5 Dry mouth 9.1 vs. 21.1 vs. 0 Nausea 4.5 vs. 9.1 vs. 0 Headache18.2 vs. 15.8 vs 5 Akathisia 4.5 vs. 21.1 vs. 0 Abnormal vision 4.5 vs. 21.1 vs. 0 Respiratory infection 18.2 vs. 5.3 vs. 0 Constipation 13.6 vs. 5.3 vs. 0 Abnormal thinking 9.1 vs. 10.5 vs. 0	26 withdrawals 16 due to AEs (0 placebo, 9 zip80, 7 zip160)	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Garakani 2008 USA	DB RCT 3 sites	Inclusion: Male and female outpatients aged 18-65 years, who met DSM-IV criteria for unipolar major depression, without psychotic features, single episode or recurrent. All patients' diagnoses were based on clinical assessments by a psychiatrist and were confirmed by the MINI. All patients required a MADRS score of >15 at both screen and baseline visits. Exclusion: if they had received an antidepressant medication for the current episode of depression or any antidepressant within 2 weeks (4 weeks if fluoxetine) of entering the study, whichever lasted longer; if they had a history of treatment-refractory depression during any episode of depression before the current episode, defined as failure to respond to adequate trials of at least two antidepressant medications or to an adequate course of electroconvulsive therapy. An adequate course of electroconvulsive therapy was defined as a minimum of 6 treatments; if they met criteria for primary diagnosis of any of the following Axis I disorders: any eating disorder, any psychotic disorder, any delirium, dementia, bipolar, or obsessive–compulsive disorder; any Axis II disorder as clinically assessed by the investigator that would interfere with the conduct of the study (e.g. severe antisocial or borderline personality and mental retardation); represented a significant risk for suicide, defined as >severe risk per Mini International Neuropsychiatric Interview or a positive response to the suicide item of the MADRS; women of childbearing potential, pregnancy, breast-feeding, or not using a medically acceptable form of contraception	quetiapine (25–100 mg/day) and fluoxetine (20–40 mg/day) vs placebo and fluoxetine (20–40 mg/day) 8 weeks duration	None

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Garakani 2008 USA	NR	MADRS at screen, baseline (study day 1),and at weeks 1, 2, 3, 4, 5, 6, 7, and 8 Barnes Akathisia Scale; Simpson Angus Scale; Anger Attacks Questionnaire; Arizona Sexual ExperiencesScale: assessed at baseline and week 8 HAS; Clinical Global Improvement (CGI); CGI-Efficacy Index: assessed weekly	Male 44.7% Mean age: 40.7 years Female 55.3% Mean age: 41.9 years Ethnicity: NR	Mean MADRS score: 30.08	NR/NR/114

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow-up/analyzed	Results	Method of adverse events assessment
Garakani 2008 USA	27/NR/114	Mixed-effects regression of MADRS, HAS, CGI-Severity,and CGI-Improvement (CGI-I) scores show that quetiapine plus fluoxetine did not achieve 50% reduction in MADRS score or improvement in HAS, CGI-Severity, and CGI-I scores from baseline sooner than the fluoxetine plus placebo group. Data not shown. CGI-Improvement shown in graph. No significant differences were observed in any of the secondary outcome measures, which included the Barnes Akathisia Scale, Simpson Angus Scale, Anger and Sexual Experience rating scales (data not shown).	Safety assessments were performed at each visit and included vital signs and reports of adverse events (AEs), along with laboratory examination, electrocardiogram, and physical examination performed at screening.

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Garakani 2008 USA	Fluoxetine/Quetiapine vs Fluoxetine: n (%) Gastrointestinal symptoms (nausea, diarrhea,and constipation): 8 (14) vs 13 (22.8) Sedation: 15 (26.3) vs 4 (7); *P*=0.006 Dizziness and lightheadedness: 10 (17.5) vs 7 (12.3) Dry mouth: 7 (12.3) vs 5 (8.8) Anxiety: 4 (7) vs 7 (12.3) Headache: 3 (5.3) vs 7 (12.3) Fatigue: 5 (8.7) vs 4 (7) Muscle and joint pain: 2 (3.5) vs 4 (7)	Total withdrawals: 27 Withdrawals due to AE: NR	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Keitner 2009 USA	DB RCT 2 centers	Inclusion - MDD; MADRS score >15; age 18–65 years; currently receiving, but failing to respond, to an adequate trial of an antidepressant medication at an adequate dose for an adequate duration; ability to read and write English. Exclusion - met criteria for bipolar I or bipolar II disorder; psychotic features; an imminent suicide risk; substance dependence or abuse in the previous three months; concurrent medical illness or history of seizures that would contraindicate use of the study medication; were receiving ECT; were pregnant or breastfeeding or currently taking herbal medications	adjunctive risperidone or placebo for the 4-week treatment trial	147 enrolled in 5 week open-label treatment, those that do not respond were randomized or had clinical proof of failure to respond
Mahmoud 2007 USA	DB RCT Multicenter (75)	Inclusion - Outpatients 18 to 65 years of age who had received antidepressant monotherapy for at least 4 weeks and met the DSM of Mental Disorders, fourth edition, criteria for unremitting major depressive disorder (single or recurrent episodes) and a CGI-S score of 4 or more at the start of both the open-label and double-blind phases **Exclusion** - pregnancy; serious suicidal risk or serious medical or neurologic illness; active substance or alcohol use disorders; or current treatment with a tricyclic antidepressant, monoamine oxidase inhibitor, mood stabilizer, antiepileptic, or a centrally acting agent for ADD/ADHD or narcolepsy.	risperidone, 1 mg/d, or placebo for 6 weeks. At 4 weeks risperidone was increased to 2 mg/d in some.	4 week run-in

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Keitner 2009 USA	Benztropine (1 mg/p.o.) for extrapyramidal side effects and Zolpidem, Zaleplon – both at 5 mg qhs as sedatives	MADRS, HAM-D, CGI-S, assessed baseline and weekly, Q-LES-Q (Baseline, weeks 2 and 4)	Mean 45 yrs 45% male 90% White	Placebo vs. risperidone MADRS 25.5 (5.4) vs. 25.8 (5.7) HAM-D 18.6 (4.3) vs. 19.5 (4.7)	246/NR/97
Mahmoud 2007 USA	Concomitant medications were allowed as necessary for medical conditions. Sedative agents (zolpidem, 2.5 to 10 mg/d, or zaleplon, 5 to 20 mg/d, as needed) for insomnia, benztropine mesylate was permitted for potential treatment-emergent motor effects	HAM-D 17, CGI-S, Q-LES-Q, the Patient Global Improvement Scale, and the Sheehan Disability Scale (SDS). At end of the open-label phase and weeks 1, 2, 4, and 6	Mean age 46 yrs 26% male 76% white 7% Hispanic 15% black 2% other	Mean time since diagnosis, 16.7 years [SD, 12.3]	463/274/274

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow-up/analyzed	Results	Method of adverse events assessment
Keitner 2009 USA	15/2/95	Placebo vs. risperidone Remission MADRS 24.2% vs. 51.6% P = 0.011 Response MADRS 33.3% vs. 54.8 P 0.049 Response HAM-D 30.3% vs. 45.2% P = 0.151	"Elicited" by researchers at weekly visits
Mahmoud 2007 USA	42/9/268	Risperidone vs. placebo % in remission 24.5 vs. 10.7 Response % 46.2 vs. 29.5 LSM (SE) CGI-S Baseline 4.4(0.08) vs. 4.4(0.08) P = 0.72 Week 6 2.9(0.08) vs. 3.5 (0.08) P < 0.001 Medication satisfaction Baseline 2.4(0.09) vs. 2.4(0.09) P = 0.64 Week 6 3.4(0.09) vs. 3.0(0.09) P < 0.001 Overall life satisfaction Baseline 2.1(0.09) vs. 2.1(0.08) P = 0.61 Week 6 3.1(0.08) vs. 2.7(0.08) P < 0.001 Patient Global Improvement Scale Week 6 2.7(0.11) vs. 3.1(0.11) P = 0.013 Sheehan Disability Scale Total score Baseline 19.9(0.61) vs 20.2(0.59) P = 0.68 Week 6 12.3(0.55) vs. 15.7(0.54) P < 0.001	Open ended questions

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Keitner 2009 USA	Placebo vs. Risperidone n (%) Any event 27 (81.80) vs. 54 (84.4) P = 0.75 Abdominal gas 2 (6.1) vs. 0 (0.0) P = 0.05 Constipation 3 (9.1) vs. 8 (12.5) P = 0.62 Dry mouth 1 (3.0) vs. 9 (14.1) P = .09 Fatigue 2 (6.1) vs. 0 (0.0) P = 0.05 Increased appetite 0 (0.0) vs. 10 (15.6) P = 0.02 Insomnia 3 (9.1) vs. 2 (3.1) 1.59 .21 Headache 5 (15.2) vs. 6 (9.4) P = 0.40 Tired 2 (6.1) vs. 0 (0.0) P = 0.05 Weight gain 1 (3.0) vs. 2 (3.1) P = 0.98	15 withdrawals due to AEs NR	
Mahmoud 2007 USA	Risperidone vs. placebo Any treatment-emergent adverse event 63 (46) vs. 72 (55) Constipation 5 (3.6) vs. 3 (2.3) Diarrhea 3 (2.2) vs. 5 (3.8) Dry mouth 7 (5.1) vs. 1 (0.8) Dyspepsia 3 (2.2) vs. 4 (3.1) Nausea 2 (1.5) vs. 6 (4.6) Fatigue 5 (3.6) vs. 0 Peripheral edema 4 (2.9) vs. 1 (0.8) Nasopharyngitis 3 (2.2) vs. 4 (3.1) Sinusitis 2 (1.5) 4 (3.1) Upper respiratory tract infection 0 3 (2.3) Weight gain 6 (4.4) vs. 2 (1.5) Arthralgia 2 (1.5) vs. 3 (2.3) Back pain 0 vs. 3 (2.3) Disturbance in attention 3 (2.2) vs. 0 Dizziness 5 (3.6) vs. 3 (2.3) Headache 12 (8.8) vs. 19 (14.5) Lethargy 1 (0.7) vs. 3 (2.3) Somnolence 7 (5.1) vs. 2 (1.5) Insomnia 6 (4.4) vs. 2 (1.5) Hypertension 0 vs. 3 (2.3)	42 withdrawals 10 due to AEs	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Marcus 2008 USA	DB RCT Multicenter (36)	Inclusion - outpatients aged 18–65 years; major depressive episode had lasted at least 8 weeks, reported an inadequate response to previous ADT, via the Antidepressant Treatment Response Questionnaire Exclusion- reported in a separate study (Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2007;68:843–853.)	adjunctive aripiprazole (mean 11 mg/day) or placebo. 6 weeks	7-28 day washout
McIntyre 2007 Canada	DB RCT Single center	Inclusion - Adults (18–65 years of age; DSM-IV diagnosis of major depression; HAM-D 17 score of > 18; CGI-S score of > 4 (moderately ill); and HAM-A 14 > 14. All had to be met both at screening and baseline, all patients had been treated for their current episode of MDD with a single SSRI/venlafaxine at a therapeutic dose for at least 6 weeks. **Exclusion** - diagnosis of substance abuse or dependence within 6 months; antipsychotic or benzodiazepine 7 days prior or a potent cytochrome P450 inhibitor or inducer 14 days prior; pregnant, breastfeeding, or at risk of suicide	Quetiapine (mean (SD) dose 182 (69) mg/day) vs. placebo	None

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Marcus 2008 USA	standard ADT	Change in MADRS and Sheehan Disability Scale, CGI-I and CGI Severity of Illness (CGI-S), the Inventory of Depressive Symptomatology Self-Report Scale (IDS-SR),21 and the Quick Inventory of Depressive Symptoms Self-Report Scale assessed weekly for the 6-week duration	Mean age 44.5 yrs 64% male 89% white 7% Black/African American 2% Asian 1% other	MADRS 26	1151/831/381
McIntyre 2007 Canada	SSRI/venlafaxine therapy for all and patients already receiving hypnotics were allowed to continue	HAM-D, HAM-A, CGI, and Global Assessment Scale (GAS) at baseline and at Weeks 1, 2, 4, 6, and 8 and DAI-10 Weeks 1, 2, 4, 6, and 8.	Mean age 44.5 years 38% male Ethnicity NR	Quetiapine vs. placebo HAM-D 23.4 (3.0) vs.. 23.2 (2.2) HAM-A 22.6 (4.5) vs. 22.6 (3.9) CGI-S 4.1 (0.3) vs. 4.1 (0.3) GAS 53.5 (4.0) vs. 53.3 (3.9)	73/NR/58

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow-up/analyzed	Results	Method of adverse events assessment
Marcus 2008 USA	57/0/381	Placebo vs. Aripiprazole Change from baseline at 6 weeks MADRS -8.5 vs.. -5.7 P = 0.001 Remission (MADRS 10 or less)15.2% vs 25.4% P = 0.016 Response (> 50 reduction in MADRS) 17.4% vs 32.4% SDS -0.7 vs. -1.3 P = 0.012 CGI-S -0.6 (0.08) vs. -1.1 (0.08) P <0.001 IDS-SR -4.6 (0.73) vs. -6.0 (0.73) P = 0.126 QIDS-SR -1.8 (0.31) vs. -2.3 (0.30) P = 0.213	Monitoring of adverse events (AEs), body weight, vital signs, labs, extrapyramidal symptoms rating scale evaluations included changes in Simpson-Angus Scale, the Abnormal Involuntary Movement Scale, and the Barnes Akathisia Clinical Assessment
McIntyre 2007 Canada	24 (11 quetiapine, 13 placebo)/2/58	Quetiapine and placebo Mean (95% CI) treatment difference HAM-D 5.7 (1.5, 9.8) HAM-A 6.6 (2.6, 10.6) HAM-D response 48% vs.28%, HAM-A response 62% vs. 28%, HAM-D remitters 31% vs. 17% HAM-A remitters 41% vs. 17%	"Adverse events (AEs) were monitored throughout the study and the frequency and type recorded."

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Marcus 2008 USA	Placebo vs. aripiprazole n(%) Akathisia 8 (4.2) vs. 49 (25.9) Fatigue 7 (3.7) vs. 19 (10.1) Restlessness 1 (0.5) vs. 18 (9.5) Headache 20 (10.5) vs. 17 (9.0) Insomnia 3 (1.6) vs. 14 (7.4) Somnolence 7 (3.7) vs. 13 (6.9) Tremor 5 (2.6) vs. 12 (6.3) Constipation 5 (2.6) vs. 10 (5.3) Nausea 8 (4.2) vs. 10 (5.3)	57 withdrawals 9 due to AEs	
McIntyre 2007 Canada	Quetiapine vs. placebo # Sedation/ somnolence/lethargy 25 vs. 14 Dry mouth 13 vs. 4 Increased weight 10 vs. 3 Dizziness 6 vs. 7 Headache 4 vs. 8 Irritability/restlessness 4 vs. 5 Increased appetite 5 vs. 6 Insomnia 0 vs. 9 Pain 3 vs. 4 Flu-like symptoms 2 vs. 3 Dysuria 3 vs. 1 Constipation 4 vs. 0 Anxiety 0 vs. 3 Nausea 1 vs. 3 Increased dreaming/ nightmares 4 vs. 0	24 withdrawals due to AEs 11	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Reeves 2008 USA	DB RCT Single center	Inclusion - 19-60 yrs old with MDD and suicide ideation despite previous treatment with up to 2 Ads for 3 or more weeks Exclusion - severe psychotic features, another major psychiatric disorder, unstable medical conditions, pregnant or lactating	Adjunctive treatment with risperidonr0.52 to 2 mg a day or placebo for 8 weeks	NR
Schule 2007 Germany	Open label, non-randomized single-center	Inclusion: major depressive episode or bipolar disorder, depressive state, according to DSM-IV criteria; sum score of at least 18 on the 21-item version of the HAM-D; availability of normal laboratory parameters; normal electrocardiogram; normal encephalogram Exclusion: occurrence of psychotic symptoms (psychotic depression not included); major medical disorders; substance dependence or substance abuse (except for nicotine) within 12 months prior to screening; other comorbid Axis I disorders according to SM-IV; pregnant or breast-feeding female patients	mirtazapine 45 mg/day vs mirtazapine 45 mg/day plus aripiprazole 15 mg/day 4 week	at least 3 days washout

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Reeves 2008 USA	Current antidepressant treatment	Beck Scale for Suicide Ideation, MADRS, and Profile of Mood States, Barrett Impulsiveness Scale, CGI-S	Mean age 44 yrs 30% male Ethnicity NR	Mean MADRS 35.7 Subscore suicide ideation 4.3	NR/NR/24
Schule 2007 Germany	zopiclone (up to 7.5 mg/day at night) in case of sleep difficulties and lorazepam (up to 3 mg/day) in case of inner tension, anxiety or agitation	Severity of depression was estimated weekly (days 1, 7, 14, 21, 28) using the HAM-D. Clinical response was defined by a reduction of at least 50% in the HAM-D sum score after 4 weeks of treatment. Remission was defined as a score ≤ 7 in the HAM-D sum score at week 4. Mean duration of response defined by at least 50% reduction in HAM-D	mirtazapine vs mirtazapine plus aripiprazole Mean age (SD): 50.3 (15.63) vs 44.7 (12.58) Male (n): 4 vs 9 Female (n): 16 vs 11 Ethnicity: NR	mirtazapine vs mirtazapine plus aripiprazole Mean age of onset (SD): 40.95 (16.82) vs 34.85 (10.27) years Mean HAM-D (SD): 23.45 (4.27) vs 24.75 (5.4) Mean SAR-S (SD): 2.15 (3.66) vs 0.9 vs (2.55) Mean BARS (SD): 0.7 (1.38) vs 0.65 (0.99)	52/42/42

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow-up/analyzed	Results	Method of adverse events assessment
Reeves 2008 USA	5/1/23	Risperidone vs. placebo Change in CGI-S2.38 (0.41) vs. 1.23 (0.43) Change in MADRS -22.09 vs. -14.44	Vital signs, self report, AIMS and SAS
Schule 2007 Germany	0/NR/40	mirtazapine vs mirtazapine plus aripiprazole Responders: 55% vs 60%; *P*=0.749 Remission rates: 20% vs 25%; *P*=1.0 Mean duration of treatment until response (SD): 3.35 (0.12) vs 3.33 (0.12) weeks; *P*=0.776	Extrapyramidal side effects were estimated weekly using BARS and the SAR-S. In addition, the patients were physically examined weekly. All side effects and AEs reported by the patients or observed by the examiners were recorded using a four-point scale to estimate the severity. Supine blood pressure, heart rate and laboratory parameters were also measured weekly. ECG performed at day 1 and day 28.

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Reeves 2008 USA	Risperidone vs. placebo % Nausea 8.7 vs. 13.04 Heartburn 4.35 vs. 8.7 Diarrhea 8.7 vs. 13.04 Increased appetite 4.35 vs. 8.7 Dry mouth 30.43 vs. 0 Bad taste 13.04 vs. 0 Somnolende8.7 vs. 4.35 Insomnia 4.35 vs. 13.04 Delayed ejaculation 0 vs. 13.04 Headache 8.7 vs. 47.83 Dizziness 8.7 vs. 4.35	5 withdrawals due to AEs NR	
Schule 2007 Germany	mirtazapine vs mirtazapine plus aripiprazole Weight gain (SD): from 68.82 (15.9) to 70.92 (16.67)kg vs from 78.7 (21.32) to 79.61 (21.11) kg; P=0.147 Nochanges in vital parameters or other side effects of clinical relevance and no clinically significant laboratory abnormalities occurred ECG recordings did not display any relevant abnormalities No statistical effects in BARS and SAR-S	0/0	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Shelton 2005 USA and Canada	DB RCT multi-center (71 sites)	Inclusion: 18-65 years of age; meet diagnostic criteria for DSM-IV; MADRS total score ≥ 20 at both the beginning and end of the screening period; at least 1 past treatment failure to an SSRI after at least 4 weeks of therapy at a therapeutic dose (i.e., citalopram 40 mg/day, fluoxetine 40mg/day, paroxetine 40 mg/day, or sertraline 150 mg/day). These patients who subsequently failed to respond to nortriptyline during an open-label 7week lead-in phase were enrolled. Treatment failure was defined as less than 30% improvement (decrease) in MADRS total score from baseline. Exclusion: Patients with psychotic symptoms (Brief Psychiatric Rating Scale) positive item score ≥ 3) during the nortriptyline lead-in phase were not eligible for randomization; Pregnant or lactating women; patients who had received ECT within 1 month of the study or who were likely in the opinion of the investigator to require ECT during the course of the study.	Olanzapine/Fluoxetine (6/25mg/day or 12/50 mg/day) vs Olanzapine 6-12 mg/day vs Fluoxetine 25-50 mg/day vs nortriptyline 25-175 mg/day 8 week	open-label 7 week nortriptyline lead-in phase
Shelton 2001 Country: NR	DB RCT NR	Inclusion: Outpatients who met DSM-IV criteria for recurrent major depression without psychotic features and were resistant to conventional antidepressant pharmacotherapy. Treatment resistance was defined retrospectively by history of failure to respond to antidepressants of two different classes, one of which was not an SSRI, after at least 4 weeks of therapy at an acceptable therapeutic dose. Failure to respond was confirmed prospectively during a screening period in which fluoxetine was given. At entry, patients were required to score ≥20 on the 21-item Hamilton Depression Rating Scale. Exclusion: Patients with a history of psychosis, dysthymic disorder, or bipolar disorder	Olanzapine (mean 12.5 mg/day) vs fluoxetine (mean 52 mg/day) vs olanzapine/fluoxetine (mean 13.5/52 mg/day) 8 week	6-week open label screening phase with fluoxetine

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Shelton 2005 USA and Canada	Lorazepam on an as-needed basis for anxiety (≤2 mg/day) but could not be administered within 8 hours of psychiatric evaluation; Concomitant psychotherapy could be continued but not be newly started.	MADRS; CGI-S; HAS; assessed at scheduled intervals (every 2 to 5 days for the first 2 visits and weekly thereafter) or as clinically indicated. Treatment response was defined as ≥ 50% decrease from baseline to endpoint in MADRS total score during the 8-week acute treatment phase. Remission was defined as 2 consecutive MADRS total scores ≤ 8.	Mean age: 42.4 years 68% females 88% white	Olanzapine/Fluoxetine vs Olanzapine vs Fluoxetine vs nortriptyline Mean MADRS (SD): 28.5 (7.5) vs 28.4 (7.3) vs 28.4 (7.3) vs 28.8 (6.5)	NR/946 lead-in/500
Shelton 2001 Country: NR	NR	HAM-D; severity of depression subscale of the CGI; MADRS assessed weekly Responders defined as ≥50% improvement on MADRS	Mean age (SD): 42 (11) years 75% female 96% white	NR	34/NR/28

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow- up/analyzed	Results	Method of adverse events assessment
Shelton 2005 USA and Canada	98/17/500	Olanzapine/Fluoxetine vs Olanzapine vs Fluoxetine vs nortriptyline Mean change in MADRS(SE): -8.71 (0.7) vs -6.95 (0.71) vs -8.51 (0.7) vs -7.46 (0.98); *P*=NS between groups Response rate: 27.5% vs 19.3% vs 28.9% vs 30.3%; *P*=NS between groups Remission rate: 16.9% vs 12.9% vs 13.3% vs 18.2%; *P*=NS between groups Mean change in HAS from baseline (SE): -5.3 (0.5) vs -3.9 (0.5) vs -3.9 (0.6) vs -3.9 (0.8); *P*=NS between groups	Spontaneously reported treatment-emergent adverse events were recorded at each visit using the Coding Symbols and Thesaurus for Adverse Reaction Terms. Emergence of psychosis was monitored using the BPRS. Extrapyramidal symptoms were assessed with SAR-S, BARS and AIMS; assessed at scheduled intervals (every 2 to 5 days for the first 2 visits and weekly thereafter) or as clinically indicated.
Shelton 2001 Country: NR	6/NR/28	Olanzapine vs fluoxetine vs olanzapine/fluoxetine Mean change in MADRS: -2.8 vs -1.2 vs -13.6; *P*=0.03 for combination vs olanzepine; *P*=0.006 for combination vs fluoxetine Mean change in HAM-D: -5.9 vs -3.8 vs -11.7; *P*=0.03 for combination vs olanzapine Responders: 0% vs 10% vs 60%; *P*=0.03 for combination vs olanzapine	AEs, vital signs, laboratory analysis, incidence of extrapyramidal symptoms

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Shelton 2005 USA and Canada	Olanzapine/Fluoxetine vs Olanzapine vs Fluoxetine vs nortriptyline % patients: 88% vs 86% vs 84% vs 85% Weight change (SD): +3.28 (3.5) vs +2.94 (2.98) vs -1.42 (2.61) vs +0.8 (3.06) kg No overall statistically significant differences amonth groups in mean change SAR-S, BARS, or AIMS (no data provided)	Total withdrawals: 98 Withdrawals due to AEs: 30	
Shelton 2001 Country: NR	Olanzapine vs fluoxetine vs olanzapine/fluoxetine Weight gain (SD): 6.07 (2.57) vs 0.88 (1.33) vs 6.67 (4.54) kg "The most frequently reported significant adverse events included somnolence, increased appetite, asthenia, weight gain, headache, dry mouth, and nervousness" "No clinically significant changes in vital signs or laboratory analytes were found among treatment groups, nor were there significant differences in the incidence of extrapyramidal symptoms"	Total Withdrawals: 6 Withdrawals due to AEs: 1	

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Study design Setting	Inclusion/exclusion criteria	Interventions	Run-in/washout period
Weisler 2009 USA	DB RCT Multicenter (38)	Inclusion - 18 to 65 yrs; outpatients diagnosed with MDD, single or recurrent: HAM-D of at least 22 and HAM-D item 1 2 or more at enrollment and randomization. **Exclusion** - Axis 1 disorder other than MDSD, Axis 2 impacting current psychiatric status; duration of current episode less than 4 weeks or greater than 12 months; 2 failed treatments during current episode; substance abuse/dependence; clinically significant medical illness; suicide or homicide risk	Quetiapine 50 vs. 150 vs 300 vs. placebo for 6 weeks plus 2 week taper	7 day washout
Yargic 2004 Turkey	Single blind (patient) RCT 3 centers	Inclusion - 18 to 65 years) diagnosed as major depression HAM-D scores on items 10 and 11 (associated with anxiety) > 2and HAM-A score > 26 which indicate depression associated with anxiety. **Exclusion** - HAM-D score on item 3 (related to suicide) >2, any psychotic disorder, treatment with any psychotropic medication in the last month, severe or chronic physical illnesses, abnormal results in routine hematological, biochemical, thyroid function tests or urinalysis, history of manic episodes, history of alcohol/substance abuse, pregnancy and lactation.	paroxetine vs. paroxetine+ quetiapine Quetiapine 200 mg/day and paroxetine to 60 mg/day	None

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Weisler 2009 USA	Lorazepam, zolpidem tartrate, zaleplon, zopiclone, chloral hydrate and anticholinergics	MADRS, HAM-D, CGI-S, CGI-I, HAM-A, Q-LES-Q and Pittsburgh Sleep Quality Index assessed baseline, weeks 1,2,4,6	Mean age 41 yrs 41% male 73% White 23% Black 1% Asian 3% other	Single episode 14% Recurrent 86%	1515/1163/723
Yargic 2004 Turkey	Yes, specifics not reported	HAM-D, HAM-A, CGI scales assessed at baseline and weeks 1, 2, 4, 6 and 8.	Mean age 35 yrs 26% male Ethnicity NR	Previous depressive episode 54%	NR/NR/120

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Number withdrawn/ lost to follow-up/analyzed	Results	Method of adverse events assessment
Weisler 2009 USA	212/50/700	Quetiapine 50 vs. 150 vs 300 vs. placebo (P is vs. placebo) LSM mean change MADRS -13.56; P<.05 vs. -14.50; P<.01) vs. -14.18; P<.01) vs. -11.07 HAM-D -12.35 (P .094) vs. -12.05 (P < 0.05) vs.. -12.65 (P < 0.05) HAM-A -8.11 (P < .05) vs. -8.34 (P < 0.01) vs. -8.2 (P < 0.05) vs. -6.64 CGI-S -1.43 (P< 0.05) vs. -1.5 (P < 0.01) vs. -1.49 (P < 0.01) vs. -1.11 CGI-I response (%) 52.8 (P < 0.01) vs. 54.2 (P < 0.01) vs. 54% (P < 0.01) vs. 39.3	AEs reported throughout study and BARS, AIMS, SAS
Yargic 2004 Turkey	28/8/112	Paroxetine vs. Paroxetine /quetiapine Change in HAM-D -14.6 (8.0) vs. -21.9(7.7) P = 0.001 Change in HAM-A -19.9 (10.4) vs. -26.7 (8.4) P = 0.003	Direct questioning based on a symptom/AE list, together with spontaneous reports by the patient

Evidence Table 25. Randomized controlled trials of patients with major depressive disorder

Author Year Country Trial name (quality rating)	Adverse events reported	Total withdrawals Withdrawals due to adverse events	Comments
Weisler 2009 USA	Quetiapine 50 vs. 150 vs 300 vs. placebo Incidence of AEs 79.6 vs 85.2 vs 88.3 vs 69.6 Dry mouth 22.1 vs. 37.5 vs. 41.3 vs. 8.8 Sedation 27.1 vs. 35.8 vs. 30.7 vs. 6.1 Somnolence 18.2 vs. 19.9 vs. 29.1 vs. 11 Headache 12.2 vs. 13.6 vs. 14.5 vs. 14.9 Dizziness 8.8 vs. 10.8 vs. 10.6 vs. 5.5 Constipation 7.2 vs 8.5 vs 8.9 vs 2.8 Nausea 7.7 vs 8.5 vs 8.9 vs 6.1 Insomnia 5 vs 6.8 vs 6.7 vs 7.7 Vomiting 1.7 vs 2.3 vs 6.7 vs 2.2 Fatigue 6.1 vs 8.0 vs 6.1 vs4.4 Back pain 1.7 vs 5.7 5.0 vs2.2 Increased appetite 4.4 vs 5.1 vs4.5 vs 3.9 Diarrhea 6.6 vs 6.3 vs 3.4 vs 8.8 Irritability 6.1 vs 5.7 vs 3.4 vs 3.9 Dyspepsia 2.2 vs 5.7 vs 2.8 vs 2.8 Myalgia 4.4 vs 7.4 vs 7.4 2.2 vs 1.7	212 withdrawal 85 due to AEs	
Yargic 2004 Turkey	Paroxetine vs. Paroxetine /quetiapine Insomnia 11.9% vs. 0 P = 0.018 Increased appetite 2.4% vs. 20.4 Increased anxiety (at week 4) 31.3% 2% P = 0.048	28 withdrawals 11 due to AEs	

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Alexopoulos 2008	Unclear, "random sequences generated by statistician"	Yes	Yes	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
AstraZeneca Study #D1448C0003	NR	NR	Yes	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Astrazeneca Study #D1448C0004	NR	NR	Yes	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Astrazeneca Study #D1448C0005	NR	NR	Yes	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Astrazeneca Study #D1448C0006	NR	NR	Yes	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
AstraZeneca Study #D1448C0014	NR	NR	Yes	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Bauer 2009	NR	NR	Yes	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Maintenance of comparable groups
Alexopoulos 2008	Unclear - "Stated double-blind"	Yes, No, No, No	Relapse was endpoint of interest, so other withdrawals were: 9% in risperidone group and 12.9% in placebo group	Unclear
AstraZeneca Study #D1448C0003	Unclear - "Stated double-blind"	Yes, No, No, No	No/Yes 71% completed 8-week randomized treatment period	Unclear
Astrazeneca Study #D1448C0004	Unclear - "Stated double-blind"	Yes, No, No, No	No/Yes 73% completed 8-week randomized treatment period	Unclear
Astrazeneca Study #D1448C0005	Unclear - "Stated double-blind"	Partially, No, Yes, No	Unclear, Unclear	Unclear
Astrazeneca Study #D1448C0006	Unclear - "Stated double-blind"	Partially, No, Yes, No	Yes/No Completion rate was 84% for placebo and 70% for quetiapine 300 mg	Unclear
AstraZeneca Study #D1448C0014	Unclear - "Stated double-blind"	Yes, No, No, No	No/Yes 76% completed 9-week randomized treatment period	Unclear
Bauer 2009	Unclear - "Stated double-blind"	Yes, No, No, No	No/No	Unclear

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Intention-to-treat (ITT) analysis	Funding	Quality Rating
Alexopoulos 2008	Yes	Janssen	Fair
AstraZeneca Study #D1448C0003	Excluded 11/310 (3.5%)	AstraZeneca	Fair
Astrazeneca Study #D1448C0004	Excluded 12/471 (2.5%)	AstraZeneca	Fair
Astrazeneca Study #D1448C0005	Yes, included 99%	AstraZeneca	Fair
Astrazeneca Study #D1448C0006	Yes, using LOCF included 97%	AstraZeneca	Fair
AstraZeneca Study #D1448C0014	Excluded 3/338 (≤ 1%)	AstraZeneca	Fair
Bauer 2009	Yes	AstraZeneca	Fair

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Berman 2007	NR	NR		Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Berman 2009	NR	NR	Mostly: more females in aripiprazole group	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Chaput 2008	Unclear	Unclear	Yes	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Corya 2006	NR	NR	Yes	Yes	Yes	Yes
Cutler 2009	Yes	Yes	Lower proportion female in quetiapine XR 300 mg group (51%) compared to in other groups (range, 62% to 64%)	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Dunner 2007	NR	NR	Yes	Yes	Yes	Open-Label

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Maintenance of comparable groups
Berman 2007	Unclear - "Stated double-blind"	Yes, No, Yes, No	No/No	Yes
Berman 2009	Yes	Yes, No, No, No	No/No	Unclear
Chaput 2008	Yes	Yes, No, No, No	9% in quetiapine group vs 55% in placebo group dropped	No
Corya 2006	Yes	Yes, No, Yes, No	No, No	Yes
Cutler 2009	Yes	Yes, No, No, No	Yes/Yes Greater proportion of discontinuations in quetiapine XR 150 mg group (34%) vs other groups (range, 21% to 30%)	Unclear
Dunner 2007	Open-Label	Yes, No, No, No	Yes/Yes 25% withdrew from sertraline group; 50% withdrew from sertraline + ziprasidone 80mg group; 53% withdrew from sertraline + ziprasidone 160mg	Unclear

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Intention-to-treat (ITT) analysis	Funding	Quality Rating
Berman 2007	No - not all randomized included	Bristol-Myers Squibb Co, Otsuka Pharmaceutical Co Ltd	Fair
Berman 2009	Yes	Bristol-Myers Squibb	Fair
Chaput 2008	Yes	AstraZeneca	Fair
Corya 2006	No; excluded 5%	Eli Lilly	Fair
Cutler 2009	Excluded 25/612 (4%)	AstraZeneca	Fair
Dunner 2007	Yes	Pfizer	Fair

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Garakani 2008	NR	NR	NR	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Keitner 2009	NR	NR	Yes	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Mahmoud 2007	Yes	Yes	Yes	Yes	Yes	Yes
Marcus 2008	NR	NR	Yes	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
McIntyre 2007	NR	NR	No: placebo group was 7kq higher and had a mean dosage of venlafaxine higher than the quetiapine group	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Reeves 2008	NR	NR	More women in the risperidone group (92% vs 45%; N=24)	Yes	Unclear - "Stated double-blind"	Unclear - "Stated double-blind"
Shelton 2001	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Maintenance of comparable groups
Garakani 2008	Yes	Yes, No, No, No	No/No	Unclear
Keitner 2009	Unclear - "Stated double-blind"	Yes (somewhat), No, No, No	Unclear	Unclear
Mahmoud 2007	Yes	Yes, No, No, No	No/No	Unclear
Marcus 2008	Unclear - "Stated double-blind"	Yes, No, No, No	No/No	Unclear
McIntyre 2007	Unclear - "Stated double-blind"	Yes, No, No, No	62% in quetiapine group completed 55% in placebo group completed	Unclear
Reeves 2008	Unclear - "Stated double-blind"	Yes, No, No, No	No/No	Yes
Shelton 2001	Yes	Yes, No, No, No	No, No	Yes

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Intention-to-treat (ITT) analysis	Funding	Quality Rating
Garakani 2008	Yes for response; no for remission (excluded 24% who did not complete all 8 weeks)	AstraZeneca	Fair
Keitner 2009	Yes	Janssen	Fair
Mahmoud 2007	Yes: ITT population comprised of 268/274 (98%) who received ≥ 1 dose of study medication; imputation method for early disconuations was LOCF and MMRM	Janssen	Good
Marcus 2008	NR	Bristol-Myers Squibb	Fair
McIntyre 2007	Yes	AstraZeneca	Fair
Reeves 2008	Excluded 1 subject who dropped out before first follow-up visit	Orth-McNeil Janssen Scientific Affairs, LLC	Fair
Shelton 2001	Yes	Eli Lilly	Fair

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Shelton 2005	NR	NR	Yes	Yes	Yes	Yes
Shule 2007	Not randomized; assignment was by doctor discretion	N/A	No significant differences, but trend for more females (80% vs 55%) with a first depressive episode (50% vs 20%) in monotherapy group	Yes	Open-Label	Open-Label
Thase 2007-Study 1	NR	NR	Yes	Yes	Yes	Yes
Thase 2007-Study 2	NR	NR	Yes	Yes	Yes	Yes
Weisler 2009	Yes	NR	Yes	Yes	Yes	Yes
Yargic 2004	Unclear, "fixed block size of four list"	NR	Yes	Yes	Single-blind	Single-bilnd

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Maintenance of comparable groups
Shelton 2005	Yes	Yes, No, Yes, No	No, NO	Yes
Shule 2007	Open-Label	Yes, No, No, No	No/No	Yes
Thase 2007-Study 1	Yes	Pooled data from Study 1 and Study 2 reported for attrition and adherence only	Significantly higher pooled rate of attrition for the olanzapine group (36%) vs the olanzapine/fluoxetine combination group (26%) and the fluoxetine (19%) ; attrition for study 1 only NR	Unclear
Thase 2007-Study 2	Yes	Pooled data from Study 1 and Study 2 reported for attrition and adherence only	Significantly higher pooled rate of attrition for the olanzapine group (36%) vs the olanzapine/fluoxetine combination group (26%) and the fluoxetine (19%) ; attrition for study 1 only NR	Unclear
Weisler 2009	Yes	Yes, No, No, No	No/Yes Discontinuation rates ranged from 26% to 33% across treatment groups	Unclear
Yargic 2004	Yes	Yes, No, No, No	No/No	Unclear

Evidence Table 26. Quality assessment of randomized controlled trials of patients with major depressive disorder

Author, Year Country	Intention-to-treat (ITT) analysis	Funding	Quality Rating
Shelton 2005		Eli Lilly	Fair
Shule 2007	Yes	Bristol-Myers Squibb	Poor
Thase 2007-Study 1	No, pooled rate of exclusions=1%;	Eli Lilly	Fair
Thase 2007-Study 2	No, pooled rate of exclusions=1%;	Eli Lilly	Fair
Weisler 2009	Excluded 21/723 (3%)	AstraZeneca	Fair
Yargic 2004	Yes	NR	Fair

Evidence Table 27. Observational studies in patients with major depressive disorder

Author, year Country	Study design	Time period covered Data source	Sample size	Population characteristics
Barbee 2004	Retrospective chart review	Time period covered: NR Data source: Charts from a fee-for-service psychiatric outpatient clinic	76 medication trials in 49 patients	Patients treated with 1+ doses of olanzapine, risperidone, quetiapine, or ziprasidone as augmentation for treatment-resistant, nonpsychotic MDD after being treated with an established antidepressant medication regimen for a minimum of 6 weeks % Male: 30.6
Seo 2009	Prospective cohort study	Time period covered: 2002-2006 Data source: patients admitted to a psychiatric inpatient unit for the treatment of MDD at two university hospitals in Seoul and Daejeon, Korea	AAP group: n=100 Non-AAP group: n=172	Patients with MDD who were treated with only one antidepressant during the admission period (non-AAP group) or were treated with augmentation with an APP for >2 weeks (AAP group) Sex (% male): 22 Mean age (y ± SD): 51.9±16.5 Duration of illness (y ± SD): 7.4±8.2

Evidence Table 27. Observational studies in patients with major depressive disorder

Author, year Country	Efficacy/effectiveness outcomes	Harms
Barbee 2004	Mean treatment duration (w): Olanzapine: 19.59 ± 21.66 (range 1-92 w) Risperidone: 35.86 ± 32.08 (range 4-94 w) Quetiapine: 17.94 ± 21.94 (range 2-74 w) Ziprasidone: 9.40 ± 10.97 (range 1-28 w)	Withdrawals (%) due to weight gain: Olanzapine: 43 Risperidone: 0 Quetiapine: 10 Ziprasidone: 14
Seo 2009	NR	Comparisons of weight changes in subjects of the AAP group using different combination therapies: n (%)/Change in weight (kg ± SD)/Statistics*/P-value SSRIs + olanzapine: 25 (25.0)/4.21±1.90/21.934/<0.001** SSRIs + quetiapine: 15 (15.0)/2.89±1.40/0.002/0.962 SSRIs + risperidone: 11 (11.0)/2.40±2.38/2.356/0.128 Mirtazapine + olanzapine: 10 (10.0)/2.44±1.26/1.734/0.191 Mirtazapine + quetiapine: 9 (8.3)/1.99±1.46/5.242/0.024** Venlafaxine + quetiapine: 8 (8.0)/3.16±1.81/0.017/0.896 Venlafaxine + olanzapine: 16 (16.0)/-/-/- Others: *ANCOVA was performed with duration of AAP prescription and duration of illness as covariates. P-value was derived from t-statistic based on the change in weight according to each type medications versus all others combined **P<0.05

Evidence Table 27. Observational studies in patients with major depressive disorder

Author, year Country	Comments	Funder
Barbee 2004	Does not report all-cause discontinuations and did not analyze between-drug differences in duration of treatment	Eli Lilly and Co.
Seo 2009		Korea Health 21 R&D Project, Ministry of Health, Welfare and Family Affairs, Republic of Korea

Evidence Table 28. Quality assessment of observational studies in major depressive disorder

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Barbee 2004	Yes	No	No	No	Unclear	No	No for olanzapine, quetiapine, and ziprasidone. Yes for risperidone.	Poor
Seo 2009	Unclear whether 272 enrolled represented all eligible patients admitted between 2002 and 2006	Yes	Yes	Yes	Yes	Yes for duration of atypical antipsychotic treatment and illness duration	No	Fair

Evidence Table 29. Trials in adolescent schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/washout period
Arango 2009 Spain	50	Open-label RCT Psychiatric hospital	Inclusion - with a diagnosis of psychosis (i.e., schizophrenia or any other psychotic disorder according to DSM-IV criteria; first episode of psychosis before the age of 18, lasting less than 1 year after onset of the first positive symptom; 12–18 years of age. Exclusion - if the psychotic symptoms appeared to result from acute intoxication or withdrawal; DSM-IV criteria for any substance abuse, mental retardation, or pervasive developmental disorder, suffered from any organic central nervous system disorder, history of traumatic brain injury with loss of consciousness, were pregnant or breast-feeding, or were taking olanzapine or quetiapine before enrolment.	Quetiapine vs. olanzapine 532.8 (459.6) vs. 9.7 (6.5) mg/day 180 days	None

Evidence Table 29. Trials in adolescent schizophrenia

Author, year Country Trial name	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Arango 2009 Spain	Yes except for other anti-psychotics	Mean age 16 yrs 78% male 82% Caucasian 4% Caribbean Black 12% Hispanic 2% Gipsy	Schizophrenia 34% Bipolar disorder 26% Other psychoses 40%	NR/NR/50	17/7/50

Evidence Table 29. Trials in adolescent schizophrenia

Author, year Country Trial name	Outcome scales	Method of outcome assessment and timing of assessment	Results
Arango 2009 Spain	PANSS; Global Assessment Scale for Children (C-GAS), Clinical Global Impression-Severity score (CGI-S), Hamilton Depression Rating Scale (HDRS-21) , and the Young Rating Mania Scale (YRMS) and the strengths and difficulties questionnaire (SDQ)	All scales were administered by four board-certified psychiatrists with clinical experience with children and adolescents. Assessed at baseline, visit 1 (day 7), visit 2 (day 15), visit 3 (day 30), visit 4 (day 90), and visit 5 (day 180), except for the SDQ scale (in its three versions), which was administered only at baseline and end of study.	Quetiapine baseline/6 months vs. olanzapine baseline/6 months CGI 5.04 ± 1.30 / 2.96 ± 1.40 vs 5.46 ± 0.86 / 3.54 ± 1.30 P = 0.605 YOUNG 15.70 ± 12.85 / 5.50 ± 6.39 vs. 18.73 ± 12.69 / 6.34 ± 9.62 P = 0.464 HAMILTON 17.27 ± 9.69 / 8.00 ± 6.70 vs. 17.83 ± 10.03 / 9.12 ± 7.91 P = 0.660 GAF 41.17 ± 15.56 / 67.79 ± 16.79 vs. 37.58 ± 17.33 / 61.88 ± 16.01 P = 0.118 PANSS Positive 23.25 ± 7.25 / 15.08 ± 4.07 26 vs. 12 ± 4.10 / 14.04 ± 4.75 P = 0.118 PANSS Negative 21.88 ± 6.835 / 16.29 ± 5.15 vs. 26.58 ± 8.34 / 22.15 ± 7.24 P = 0.340 PANSS General 46.05 ± 11.26 /34.45 ± 9.89 vs. 52.96 ± 10.84 / 35.42 ± 8.88 P = 0.093 PANSS Total 91.05 ± 21.42 / 67.29 ± 17.86 vs. 105.65 ± 19.97 / 71.62 ± 17.33 P = 0.41

Evidence Table 29. Trials in adolescent schizophrenia

Author, year Country Trial name	Methods of adverse event assessments	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Arango 2009 Spain	Weight changes (measured as increase in kilograms and body mass index (BMI)), UKU scale of adverse reactions , Barnes Akathisia Scale, and Simpson Neurological Rating Scale for extrapyramidal side effects, blood cell counts, electrolytes, renal function, liver function, energy metabolism (glucose, HgbA1c, lipid profile), prolactin, and EKG were performed at baseline and at each visit.	Quetiapine vs. olanzapine n (%) Concentration difficulties 16 (67) vs. 18 (72) Asthenia/lassitude/increased fatigability 19 (79) vs. 19 (73) Sleepiness/sedation 19 (79) vs. 21 (84) Failing memory 14 (58)vs. 12 (52) Depression 9 (37) vs. 11 (44) Tension/inner unrest 15 (62) vs. 13 (54) Increased duration of sleep 11 (46) vs. 12 (48) Reduced duration of sleep 4 (17) vs. 6 (25) Increased dream activity 9 (39) vs. 6 (26) Emotional indifference 7 (29) vs. 14 (56) Rigidity 4 (17) vs. 7 (29) P < 0.05 Hypokinesia/akinesia 11 (46) vs. 14 (54) Tremor 7 (37 vs. 13 (50) Akathisia 6 (26) vs. 8 (32) Accommodation disturbances 6 (26) vs. 7 (32) Increased salivation 10 (42) vs. 13 (52) Reduced salivation 9 (39) vs. 2 (8) Constipation 10 (42) vs. 7 (27) Polyuria/polydipsia 7 (30) vs. 8 (31) Orthostatic dizziness 3 (13) vs. 5 (21) Palpitations/tachycardia 11 (46) vs. 8 (35) Increased tendency to sweat 8 (33) vs. 7 (28) Weight gain 13 (72) vs. 20 (91) Amenorrhea 1 (20) vs. 4 (50) Increased sexual desire 1 (6) vs. 5 (28) Dry vagina 0 (0) vs. 2 (22) Tension headache 6 (25) vs. 6 (24) Weight gain 15.5 kg, vs. 5.4 kg,	17 withdrawals 0 due to AEs

Evidence Table 29. Trials in adolescent schizophrenia

Author, year Country Trial name	N	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)	Run-in/washout period
Gothelf 2003 Israel	43	Open-label clinical trial (i.e. not randomized) Two mental health centers	Adolescents with a diagnosis of schizophrenia was established according to DSM-IV criteria	Risperidone 3.3 (1.1) mg/day (range 1–5), for olanzapine 12.9 (3.1) mg/day (range 10–20), and for haloperidol 8.3 (3.8) mg/day (range 5–15). Duration 8 weeks	Washout of neuroleptics mean 4.8 to 6.5 days

Evidence Table 29. Trials in adolescent schizophrenia

Author, year Country Trial name	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Gothelf 2003 Israel	Lorazepam and anticholinergic agents	Mean age 17 yrs 63% male Ethnicity NR	Paranoid 49% Undifferentiated 30% Disorganized 21%	NR/NR/43	4/0/39

Evidence Table 29. Trials in adolescent schizophrenia

Author, year Country Trial name	Outcome scales	Method of outcome assessment and timing of assessment	Results
Gothelf 2003 Israel	PANSS	The clinical assessment was carried out by two senior child psychiatry fellows, at baseline, just before initiation of the antipsychotic medication, and after 4 and 8 weeks of treatment	Baseline / 8 weeks Positive symptoms Risperidone 17.4 (6.9) / 13.2 (3.8) Olanzapine 15.0 (4.9) / 13.3 (8.0) Haloperidol 21.3 (8.9) / 13.0 (5.8) Negative symptoms Risperidone 24.2 (9.3) / 20.8 (8.4) Olanzapine 18.1 (11.0) / 14.9 (8.0) Haloperidol 20.3 (8.0) / 16.4 (8.5) Total Scores Risperidone 90.2 (26.4) / 73.9 (19.1) Olanzapine 71.6 (23.8) / 61.6 (28.4) Haloperidol 86.1 (24.4) / 66.3 (21.8) Effect of Week F(2,72) 12.7, p 0.001

Evidence Table 29. Trials in adolescent schizophrenia

Author, year Country Trial name	Methods of adverse event assessments	Adverse events	Total number of withdrawals; withdrawals due to adverse events
Gothelf 2003 Israel	Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale	Risperidone vs. Olanzapine vs. Haloperidol n (%) Concentration difficulties 2 (11.8) vs. 7 (36.8) vs. 3 (42.9) Increased fatigability 2 (11.8) vs. 8 (42.1) vs. 5 (71.4) Sleepiness/sedation 3 (17.6) vs. 9 (47.4) vs. 3 (42.9) Failing memory 2 (11.8) vs. 7 (36.8) vs. 2 (28.6) Depression 2 (11.8) vs. 5 (26.3) vs. 5 (71.4) Tension/inner rest 3 (17.6) vs. 7 (36.8) vs. 2 (28.6) Increased duration of sleep 4 (23.5) vs. 9 (47.4) vs. 3 (42.9) Reduced duration of sleep 1 (5.9) vs. 4 (21.1) vs. 0 Increased dream activity 1 (5.9) vs. 4 (21.4) vs. 0 Accommodation disturbances 1 (5.9) vs. 2 (10.5) vs. 0 Increased salivation 5 (29.4) vs. 4 (21.1) vs. 1 (14.3) Reduced salivation 0 vs. 1 (5.3) vs. 1 (14.3) Nausea/vomiting 1 (5.9) vs. 2 (10.5) vs. 1 (14.3) Constipation 1 (5.9) vs. 3 (15.8) vs. 2 (28.6) Micturition disturbances 3 (17.6) vs. 1 (5.3) vs. 1 (14.3) Polyuria/polydipsia 3 (17.6) vs. 2 (10.5) vs. 2 (28.6) Orthostatic dizziness 4 (23.5) vs. 3 (15.8) vs. 1 (14.3) Palpitations/tachycardia 2 (11.8) vs. 4 (21.1) vs. 0 Pruritus 0 vs. 3 (15.8) vs. 0 Diminished sexual desire 1 (5.9) vs. 4 (21.1) vs. 1 (14.3)	4 withdrawals 0 due to AEs

Evidence Table 30. Observational studies in youths

Author, year Country	Study design	Time period covered, Data source	Sample size	Population characteristics	Efficacy/Effectiveness outcomes
Correll, 2009 Queens, New York	Non-randomized prospective cohort study	Between December 2001 and September 2007 Patients recruited from pediatric inpatient and outpatient clinics	338 patients enrolled (aripiprazole n=47; olanzapine n=52; quetiapine n=45; risperidone n=168; comparison group n=20) analyzed patients n=272	Youth naive to antipsychotic medication and a psychiatric comparison group consisting of patients who refused or discontinued taking antipsychotic medications within 4 weeks of starting. Age of 4 to 19 years and 1 week or less of lifetime antipsychotic treatment; psychiatric illness prompting antipsychotic medication initiation; and consent, or baseline anthropometric and biochemical assessments obtained within 7 days of antipsychotic medication initiation Mean age (SD): 13.9 (3.6) years Male: 57% White: 48.5% Black: 25.9% Hispanic: 8.9% Asian: 4.1% Mixed: 12.5% Mean weight: 53.5 kg	NR
Fleischhaker, 2008 Germany	Prospective Cohort Study	From July 1999 to October 2003 Four child and adolescent psychiatric departments in four mental health centers in Germany (Aachen, Freiburg, Marburg, and Wuerzburg)	61 inpatients considered for inclusion Final study sample n=33 (clozapine n=15; olanzapine n=8; risperidone n=10)	clozapine vs olanzapine vs risperidone Age: 17.2 vs 15.7 vs 1.3 years Males: 33.3% vs 15.2% vs 24.2% Medication dose (SD): 311.7 (137.5) vs 10.2 (3.5) vs 2.6 (1.7) mg	NR

Evidence Table 30. Observational studies in youths

Author, year Country	Harms	Comments	Funder
Correll, 2009 Queens, New York	Antipsychotic medication was associated with increased weight, fat mass, BMI and waist circumference (*P* <0.001) aripiprazole vs olanzapine vs quetiapine vs risperidone vs untreated Weight change over time: 4.4 vs 8.5 vs 6.1 vs 5.3 vs 0.2 kg Weight % change of baseline: 8.1 vs 15.2 vs 10.4 vs 10.4 vs 0.7 Fat mass over time: 2.4 vs 4.1 vs 2.8 vs 2.5 vs 0.4 kg BMI change over time 1.7 vs 3 vs 2.1 vs 1.9 vs -0.003 BMI % change: 7.2 vs 14 vs 9.3 vs 9.1 vs 0.1 Waist circumference: 5.4 vs 8.6 vs 5.3 vs 5.1 vs 0.7 cm Metabolic parameter (*P <0.05) Glucose change: 0.54 vs 3.14* vs 2.64 vs 1.14 vs 0.69 mg/dL Total cholesterol change: 3.75 vs 15.58* vs 9.05* vs 3.46 vs 2.38 mg/dL LDL cholesterol change: 7.38 vs 11.54* vs 3.88 vs 0.21 vs 2.99 mg/dL HDL cholesterol change: 0.29 vs -1.27 vs -1.47 vs 0.33 vs 1.49 mg/dL Triglycerides change: -2.4 vs 24.34* vs 36.96* vs 9.74* vs -11.84 mg/dL		Supported in parts by National Institute of Health, National Alliance for Research in Schizophrenia and Depression Award, Feinstein Island Jewish Health System General Clinical Research Center, National Center for Research Resources
Fleischhaker, 2008 Germany	clozapine vs olanzapine vs risperidone All 3 groups experienced significant weight gain from baseline Weight change (SD) from baseline in kg: 9.5 (10.4); *P* <0.004 vs 16.2(8.8); *P* <0.002 vs 7.2 (5.3); *P* <0.002 The absolute (±SD) and percentage (±SD) average weight gains were significantly higher for the olanzapine group (16.2 ± 8.8 kg; 30.1 ± 18.9%) than for the clozapine (9.5 ± 10.4 kg; 14.8 ± 15.8%) and the risperidone (7.2 ± 5.3 kg; 11.5 ± 6.0%) groups. (Mean proportional weight change over the 45 weeks of study shown as figure)		Non-restricted grant from Janssen-Cilag, Neuss, Germany

Evidence Table 30. Observational studies in youths

Author, year Country	Study design	Time period covered, Data source	Sample size	Population characteristics	Efficacy/Effectiveness outcomes
Fraguas 2008	Prospective Cohort Study	Time period covered: March 2005-October 2006 Data source: The adolescent unit of the Psychiatric Department at Hospital General Universitario Gregorio Maranon, Madrid, Spain	n=66 (risperidone n=22, olanzapine n=20, quetiapine n=24)	Children and adolescents treated with a new prescription of risperidone, olanzapine, or quetiapine within the 30 days prior to enrollment and who had no history of prior lifetime antipsychotic treatment and who were treated with the new medication for 6 months Sex (% male): 66.7 Mean age (y ± SD): 15.2 ±2.9	NR

Evidence Table 30. Observational studies in youths

Author, year Country	Harms	Comments	Funder
Fraguas 2008	Baseline and outcome measurements after 6 months of antipsychotic treatment (baseline/change): Risperidone (Mean ±SD) Weight (kg): 57.5±20.3/5.0±4.8** BMI (kg/m2): 21.8±4.5/1.4±1.8** BMI z score: 0.56±1.41/0.48±0.73** Olanzapine (Mean ±SD) Weight (kg): 61.7±15.1/11.1±7.8** BMI (kg/m2): 22.7±5.2/3.7±2.7** BMI z score: 0.26±1.49/1.10±0.82** Quetiapine (Mean ±SD) Weight (kg): 60.5±11.4/2.5±6.8 BMI (kg/m2): 21.5±3.2/0.9±2.7 BMI z score: -0.12±0.97/0.27±0.86 All Subjects (Mean ±SD) Weight (kg): 59.9±15.8/6.0±7.4** BMI (kg/m2): 22.0±4.3/1.9±2.7** BMI z score: 0.22±1.31/0.59±0.87** **P<0.01 (Wilcoxon) **Change score between treatment groupsa:** Risperidone-Olanzapine Weight (kg): p=0.037 BMI (kg/m2): p=0.46 BMI z score: NS Risperidone-Quetiapine Weight (kg): NS BMI (kg/m2): NS BMI z score: NS Olanzapine-Quetiapine Weight (kg): p<0.001 BMI (kg/m2): p<0.001 BMI z score: p=0.001 aANCOVA Sidak post hoc adjusted for multiple comparisons. Analysis of differences in change score between treatment groups were done by means of ANCOVA, controlling for age, baseline BMI, z score, psychosis, and duration of prior total lifetime antipsychotic usage		Spanish Ministry of Health, Instituto de Salud Carlos III, RETICS, Fondo de Investigacion Sanitaria, Asociacion adrilena de Salud Mental, NARSAD 2005: Independent Investigator Award

Evidence Table 30. Observational studies in youths

Author, year Country	Harms	Comments	Funder
Fraguas 2008	**Risk for adverse health outcome (baseline/month 6):** Risperidone (%) BMI ≥ 95th percentile: 13.6/31.8 BMI ≥ 85th percentile: 27.3/40.9 Weight gain (≥ 0.5 increasein BMI z score): --/50.0 Olanzapine (n, %) BMI ≥ 95th percentile: 10.0/50.0 BMI ≥ 85th percentile: 20.0/60.0 Weight gain (≥ 0.5 increasein BMI z score): --/75.0 Quetiapine (n, %) BMI ≥ 95th percentile: 4.2/8.3 BMI ≥ 85th percentile: 12.5/20.8 Weight gain (≥ 0.5 increasein BMI z score): --/29.2 All Subjects (n, %) BMI ≥ 95th percentile: 10.6/28.8 BMI ≥ 85th percentile: 19.7/39.4 Weight gain (≥ 0.5 increasein BMI z score): --/50.0 **Change score between treatment groupsb:** BMI ≥ 95th percentile: p=0.091 BMI ≥ 85th percentile: p=0.048c Weight gain (≥ 0.5 increasein BMI z score): p=0.010d cDifference between baseline and month 6 in having BMI ≥ 85th percentile post hoc (Fisher exact test when needed) comparisons: risperidone-olanzapine, p=0.035; risperidone-quetiapine, p=0.625; olanzapine-quetiapine, p=0.049 Difference in weight gain (≥ 0.5 increasein BMI z score) post hoc (Fisher exact test when needed) comparisons: risperidone-olanzapine, p=0.096; risperidone-quetiapine, p=0.148; olanzapine-quetiapine, p=0.002		

Evidence Table 31. Quality assessment of observational studies in youths

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Correll 2009 (SATIETY)	Unclear; 173/505 (34%) who refused to participate or were ineligible had less autism-spectrum disorders, substance abuse comorbidity, and mixed ethnicity	18% excluded from analysis overall due to lack of post-baseline assessment 20% excluded from analysis for quetiapine and risperidone, vs 13% for aripiprazole and olanzapine	Yes	Yes
Fleischhaker 2006	Unclear; distribution across comparison groups of different diagnoses, prior experience with antipsychotic agents and use of co-medications NR; numerically lower proportion of males in olanzapine group compared to clozapine and risperidone (56% vs 69% vs 68%)	Attrition NR; all 51 participants included in analysis	Yes	Yes
Fleischhaker 2008	Yes	46% (28/61) excluded due to early discontinuation (34%), low number of weight and height measurements (8%) and anorexia nervosa (3%); attrition per treatment group NR	Yes	Yes
Fraguas 2008	Yes	Yes/Yes Overall=28%, risperidone=42%, olanzapine=20%, quetiapine=17%	Yes	Yes

Evidence Table 31. Quality assessment of observational studies in youths

Author Year Country	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Correll 2009 (SATIETY)	Yes	Some, categorical outcomes adjusted for differences at baseline, others analyzed by stratification and other methods.	No	Fair
Fleischhaker 2006	Unclear about reliability/validity of adapted version of Dosage Record Treatment Emergent Symptom Scale (DOTES) (e.g., computerized, German language, included additional information from chart review)	Stratified by drug-naiveté and comedication use for weight gain	No; mean=7.4 weeks	Poor
Fleischhaker 2008	Yes	Yes for change in BMI standard deviation scores (SDS), unclear for others. Reported that "since the groups differed significantly in age [at baseline], several analyses were conducted to test the influence of age that is confounded with medication group. " No linear or monotone relationships found for BMI-SDS. Results for others NR.	Yes	Fair
Fraguas 2008	Yes	Yes for age, BMI z score, psychosis, duration of prior total lifetime antipsychotic usage	Yes	Fair

Evidence Table 32. Systematic reviews in bipolar disorder

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Smith 2007	To conduct a systematic review and meta-analysis of randomized, placebo-controlled trials for acute bipolar mania	1966 to March 2005	Populations: Acute bipolar mania **Interventions:** valproate semisodium, lithium, carbamazepine, lamotrigine, olanzapine, risperidone, quetiapine, aripiprazole, haloperidol, chlorpromazine, flupentixol, fluphenazine, perphenazine, prochlorperazine and zuclopenthixol **Comparators:** Placebo **Outcomes:** Changes in mania symptom scores using the Young Mania Rating Scale (YMRS) or Mania Rating Scale (MRS); mania response defined as ‡50% improvement in YMRS score; withdrawal due to any reason, due to lack of efficacy and due to an adverse event; extrapyramidal symptom scores using the Simpson Angus Scale (SAS), Barnes Akathisia Scale (BAS) and Abnormal Involuntary Movement Scale (AIMS); and weight change.	3,089	13 RCTs. Follow-up duration=3-4 wks

Evidence Table 32. Systematic reviews in bipolar disorder

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results	Adverse events
Smith 2007	Acute manic or mixed episode; in most MRS scores were ≥ 20; rapid cycling, serious suicide risk or other serious conditions were excluded from most	2 trials each for carbamazepine, haloperidol, lithium, olanzapine, quetiapine, risperidone, valproate semisodium, and aripiprazole.	Comparison to placebo, relative risk (RR), 95% confidence interval (CI): Response Aripiprazole: 1.79 (1.37, 2.34) Olanzapine: 1.67 (1.25, 2.23) Quetiapine: 1.52 (0.98, 2.37) Risperidone: 1.77 (1.43, 2.18) Withdrawal for any reason Aripiprazole: 0.82 (0.65, 1.04) Olanzapine: 0.62 (0.48, 0.80) Quetiapine: 0.64 (0.42, 0.98) Risperidone: 0.61 (0.39, 0.95)	Comparison to placebo, relative risk (RR), 95% confidence interval (CI): Withdrawal due to adverse event Aripiprazole: 1.13 (0.66, 1.93) Olanzapine: 0.79 (0.08, 8.27) Quetiapine: 1.13 (0.49, 2.60) Risperidone: 1.15 (0.61, 2.16)

Evidence Table 32. Systematic reviews in bipolar disorder

Author Year	Subgroups	Quality assessment
Smith 2007	None	1. Report clear review question, state inclusion and exclusion criteria of primary studies? Yes 2. Substantial effort to find relevant research? Yes 3. Adequate assessment of validity of included studies? Yes, based on Juni 2001 4. Sufficient detail of individual studies presented? Yes 5. Primary studies summarized appropriately? Yes Overall quality rating=Good