Drug Class Review

Atypical Antipsychotic Drugs

Final Report Update 2
Evidence Tables

June 2008

Original Report Date: January 2005
Update 1 Report Date: April 2006
A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description. Prior versions of this report can be accessed at the DERP website.

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Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Addington, 2004 DB, RCT, parallel	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 b.i.d. (N=149) or risperidone 3-5mg b.i.d. (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	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), Montogomery-Ashberg 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Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results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	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%)

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	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%

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Addington, 2004 DB, RCT, parallel	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%)	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 Randomized, 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 w/in 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 Randomized, open-label Outpatients	SANS summary score assessed at wks 8, 24 and 48 (or at early withdrawal) Monthly assesments 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 Statisitically 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 Randomized, 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 flatening, 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/unsocialbility, 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: olazapine 54%, risperidone 77% No withdrawals in either group due to AEs
Alvarez, 2006 Randomized, open-label Outpatients	EPS assessed at each visit using the EPSs questionnaire from the UKU Scale; physiological changes (ie 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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Akerele, 2007 RCT	NR	Total: 12 Due to adverse events: 0	
Alvarez, 2006 Randomized, 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	72/10	

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
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, autoimune, pulmonary, inectious 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 Double-blind, 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
Bai, 2006 Single bind RCT single center Taiwan	Symtomatic 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 sizure disorder; violent behavior; suicide risk.	Oral risperidone: 2-6 mg/day Long-acting risperidone: 20-75 mg/day Duration: 12 weeks active treatment	3 months trmt with oral risperidone	Anticholinergics and 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
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 Double-blind, 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
Bai, 2006 Single bind RCT single center Taiwan	PANSS and CGI severity at baseline weeks 4, 8 and 12	Mean age: 46.4 Male: 50% Ethnicity: NR	NR	NR

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
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 Double-blind, 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
Bai, 2006 Single bind RCT single center Taiwan	NR/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

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

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Atmaca, 2003 Inpatients	weight, body mass index, fasting serum leptin and triglyceride levels taken at baseline and endpoint	NR
Azorin, 2001 Double-blind, 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
Bai, 2006 Single bind RCT single center Taiwan	UKU	See results

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Atmaca, 2003 Inpatients	NR	NR; NR	
Azorin, 2001 Double-blind, 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
Bai, 2006 Single bind RCT single center Taiwan	NR	1 and 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
Bellack, 2004 Double-blind trial 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) RCT DB - 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.

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
Bellack, 2004 Double-blind trial 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) RCT DB - 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
Bellack, 2004 Double-blind trial 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) RCT DB - 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.

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

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Bellack, 2004 Double-blind trial Substudy within larger trial	NR	NR
Bender, 2006 (Companion to Naber 2005) RCT DB - sub sample	NR	NR

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Bellack, 2004 Double-blind trial Substudy within larger trial	NR	17% of withdrawals due to AE's but numbers per drug not clear	While some differences apparent between drugs on results for verbal score and problem solving, changes not considered clinical important by authors. Lack of ITT, low power, and poor reporting make result difficult to interpret or generalize.
Bender, 2006 (Companion to Naber 2005) RCT DB - sub sample	SAS Olazapine 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 Multi-center, 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, anticholingergic meds to treat new or worsening EPS allowed but all other uses not allowed
Bondolfi, 1998 Single-center Double-blind RCT 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 Single Center double-blind RCT (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 Multi-center, 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 Single-center Double-blind RCT 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% undifferenciated: 8.1% residual: 5.8%	NR/NR/86 clozapine: 43 risperidone: 43
Breier, 1999 Single Center double-blind RCT (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 Multi-center, 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 Single-center Double-blind RCT 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 Single Center double-blind RCT (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 Multi-center, 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 Single-center Double-blind RCT 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 Single Center double-blind RCT (NIH Clinical Center) Unclear if Inpatient	SAR-S; neuroendocrine serum level montitoring	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, coristol: changes NS

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Bitter, 2004 RCT Multi-center, 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 Single-center Double-blind RCT 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 parkisonism 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 parkisonism score: 37% vs 61% (p = 0.03) % with 0 on ESRS dysotonia: 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 comarisons. Dose of clozapine low.
Breier, 1999 Single Center double-blind RCT (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 MC, double-blind, parallel-group 28 week RCT in and outpatients Europe, North and South America	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.

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 MC, double-blind, parallel-group 28 week RCT in and outpatients Europe, North and South America	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

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Breier, 2005 MC, double-blind, parallel-group 28 week RCT in and outpatients Europe, North and South America	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 flatening, 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;

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 MC, double-blind, parallel-group 28 week RCT in and outpatients Europe, North and South America	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) 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)

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Breier, 2005 MC, double-blind, parallel-group 28 week RCT in and outpatients Europe, North and South America	Simpson-Agnus 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) -0.05 vs. 0.62 (p<0.001) Baseline to Maximum 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) 0.19 vs. 0.30 (p=0.03) Baseline to Maximum 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) 1.47 vs. 1.83 (p=0.01) Baseline to Maximum "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.

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 RCT, double-blind, 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; drease 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 pschyotropic 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

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 RCT, double-blind, 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

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Canive, 2006 RCT, double-blind, crossover	6 withdrawn/9 analyzed	Improvement ocurred 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 sesverity, 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 duirng 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; olanzapaine led to greater improvements on SANS Attention; means for all scales followed pattern of olanzapine being more efficacious; olanzapine alsom more effective for treating negative symptoms as shown by analysis perfo 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 neuropsycologic test scores.

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 RCT, double-blind, crossover	NR	NR

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Canive, 2006 RCT, double-blind, crossover	NR	Withdrawals: 6 Withdrawals due to adverse events: 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
Chan, 2007 DB, multicenter, randomized parallel study Inpatients	Nonpregnant, nonlactating; 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, randomized, 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 glucoregulatory 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 (eg, lithium, carbamazepine, valproic acid, propranolol, tricylic antidepressant, SSRI) that may influence body weight, glucose/lipid metabolism, or drug disposition. Others: 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, multicenter, randomized parallel study 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, randomized, 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

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Chan, 2007 DB, multicenter, randomized parallel study 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, randomized, open-label study to evaluate pancreatic beta-cell function	0/0/26	Risperidone group: weight, BMI, fasting glucose, fasting insulin, tryglyceride, total cholesterol, HDL, LDL, and leptin did not change significantly Olanzapine group: weight, BMI, fasting glucose, fasting insulin, tryglyceride, 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)

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, multicenter, randomized parallel study 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, randomized, open-label study to evaluate pancreatic beta-cell function	N/A	NR

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Chan, 2007 DB, multicenter, randomized parallel study Inpatients	Overall EPS realted 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, randomized, open-label study to evaluate pancreatic beta-cell function	NR	0	

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
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
Chrzanowski et al., 2006 Randomized open-label extension (Extension of Pigott 2003)	(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.

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
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
Chrzanowski et al., 2006 Randomized open-label extension (Extension of Pigott 2003)	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

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Chowdhury, 1999	14/3/NR	PANSS scores total (postive, 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 frombaseline on PANSS) total; positive; negative; general subscales: Clozapine: 80%;80%;73.33%;80%66.7%;66.7%;63.33%;66.7%
Chrzanowski et al., 2006 Randomized open-label extension (Extension of Pigott 2003)	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 pychosis 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

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

Author, year study design	Method of adverse effects assessment	Adverse effects reported
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%
Chrzanowski et al., 2006 Randomized open-label extension (Extension of Pigott 2003)	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)

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
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%)	
Chrzanowski et al., 2006 Randomized open-label extension (Extension of Pigott 2003)	SAS (aripiprazole, −0.08; olanza-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; due to Aes 8	

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
Chue, 2005 RCT, double-blind, double-dummy, multic-center, parallell, noninferiority study	Inpatients or outpatients aged 18-65; DSM-IV diagnosis of schizophrenia; total PANSS score >/= 50; no clinically relevant abnormal bichemistry, 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 tardivde dyskinesia ata study entry; histroy 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: 20-75 mg/day Duration: 12 weeks active treatment	2 week washout of antipsychotics other than risperidone; total of 8 weeks open-label run-in	Anticholnergic medication could be initiated for emergent or worsening movement disorders and propranolol coul dbe initiated for emergent or worsening akathisia; medication prescribed for sleep could be continued if used before study entry, or temazepam, zopiclone, zoplidem or chloral hydrate could be iniated 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)
Chue, 2005 RCT, double-dummy, multicenter, DB inpatients and outpatients	Inpatients and outpatients aged 18-65 years, schizophrenia, total PANSS score >50, no clinical relevant abnormal biochemistry, hematology or urninalysis, remained stable with CGI scores during last 4 weeks of risperidone run-in	N=640 All patients received flexible does of 1-6 mg of oral risperidone for first 8 weeks, then randomized to either injectable or oral (double-dummy)	2 weeks of all antipsychotics	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
Chue, 2005 RCT, double-blind, double-dummy, multic-center, parallell, 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: 0.38% Other: 4.1%	Schizophrenia type: paranoid: 61.7% undifferentiated: 17.7% residual: 14.2% disorganized: 5.6% catatonic: 0.8%	NR/779/642
Chue, 2005 RCT, double-dummy, multicenter, DB inpatients and outpatients	PANSS, CGI	Mean age: 40 years Male: 414(64.5%) White: 562(87.8%) Black: 35 (5%) Asian: 16 (2.5%) Hispanic: 1 (0%) Other: 26 (4%)	<u>Schizophrenia types:</u> Paranoid: Oral: 195(60.7) vs Inj: 200 (62.7%) Undifferentiated: Oral: 56(17.4%) vs Inj: 57(17.9%) Residual: Oral: 48(15%) vs Inj: 43(13.5%) Disorganized: Oral: 20(6.2%) vs Inj: 16(5%) Catatonic: Oral: 2(6%) vs Inj: 3(9%)	779/642/640

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Chue, 2005 RCT, double-blind, double-dummy, multic-center, parallell, noninferiority study	2 withdrawn before beginning DB treatment 541 analyzed for efficacy 640 analyzed for safety	Changes (SD) 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% ito 57.8% in oral risperidone group and from 49.2% to 57.9% in long-lasting resperidone group
Chue, 2005 RCT, double-dummy, multicenter, DB inpatients and outpatients	NR	Changes at Endpoint: Mean + SD; 95% CI: PANSS total: Oral: -6.3+ 0.7 vs Inj: -5.4 +0.7; -0.90, 2.78 Positive symptoms: Oral: -2.0+0.3 vs Inj: -1.7+0.3; -0.34,0.99 Negative symptoms: Oral: -1.6+0.3 vs Inj: -1.5+0.3; -0.59,0.82 Disorganized thoughts: Oral: -1.2+0.2 vs Inj: -1.1+0.2; -0.34, 0.71 Uncontrolled: Oral: -0.4+0.1 vs Inj: -0.3+0.1; -0.22,0.57 Anxiety/depression: Oral: -1.0+0.2 vs Inj: -0.9+0.2; -0.25,0.57

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

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Chue, 2005 RCT, double-blind, double-dummy, multic-center, parallell, noninferiority study	Patient reported, clinical lab tests (hematology, biochemistry, prolactin assay, urinalysis), vital signs, electrocardiogram, ERSR, 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 inerval 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
Chue, 2005 RCT, double-dummy, multicenter, DB inpatients and outpatients	Patient self-report	Insomnia: oral: 9% vs inj: 9.7% Anxiety: oral: 7.2% vs inj: 10% Headache: oral: 7.2% vs inj: 8.2% Psychosis: oral: 4.7% vs inj: 5.3%

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Chue, 2005 RCT, double-blind, double-dummy, multic-center, parallell, noninferiority study	NR	Total withdrawals: 113 Withdrawals due to AEs: NR	
Chue, 2005 RCT, double-dummy, multicenter, DB inpatients and outpatients	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
Ciudad, 2006 [Companion to Alvarez 2006] Multicenter, randomized, 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] Multicenter, randomized, 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] Multicenter, randomized, 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 patinets 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 disorganised 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/verymild/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] Multicenter, randomized, 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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Ciudad, 2006 [Companion to Alvarez 2006] Multicenter, randomized, 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. Cross-over 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

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. Cross-over 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

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. Cross-over 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 cholestrol (mg/dL): O: 198.0 + 44.0; C: 209.6 + 28.6 Change in total cholestrol (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 aminotranferase (AST) (IU/L): O: 23.7 + 15.9; C: 18.0 + 5.1 Change in aspartate aminotranferase (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

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. Cross-over 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 Tachcardia: 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%)

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Conley, 2003	SAS scores	6 withdrawals/ 1 withdrawal	
Kelly, 2003	decreased by 1.3 clozapine	due to adverse events	
DB. Cross-over	increased 0.3 olanzapine		
	Akathisia		
Inpatients	20% clozapine		
	20% olanzapine		
Funding: NIHM grant	1 subject received benztropine while on 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
Conley, 2005 R, parallel-group, DB X 12 weeks Inpatients -treatment resistant	Btw 18 - 65 years who met DSM-IV criteria for schizophrenia, and were treatment resistance: (def: 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
Daniel, 1996 Crossover design	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

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, 2005 R, parallel-group, 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
Daniel, 1996 Crossover design	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

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Conley, 2005 R, parallel-group, 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
Daniel, 1996 Crossover design	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)

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

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Conley, 2005 R, parallel-group, 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 ednpoint:: 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
Daniel, 1996 Crossover design	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

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Conley, 2005 R, parallel-group, 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	18/2 (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 a baseline, and no significant differences were noted after controlling for it.
Daniel, 1996 Crossover design	7/17 (41%) required Anti-EPS meds while on risperidone 0 required Anti-EPS meds while on clozapine	Total: 3/20 (15%) Due to AE: 2/20 (10%)	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.

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
Davidson, 2007 Randomized, DB, PCT, Multicenter, Parallel-group study, 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, betablockers, 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.
Dollfus, 2005 RCT, DB	Age 18-65 pts with post-psychotic depression accoring to DSM-IV criteria with maximum PANSS score of 28 and minimum total MADRS score of 16 at screening and baseline	Olanzipine 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
Davidson, 2007 Randomized, DB, PCT, Multicenter, Parallel-group study, 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	618/NR/618
Dollfus, 2005 RCT, DB	Change in MADRS from baseline; weekly assessments	Mean age: 39.3 yrs 69.7% male Ethnicity NR	Use of biperidene 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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Davidson, 2007 Randomized, DB, PCT, Multicenter, Parallel-group study, International sites	253/6/365	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. PNASS 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)
Dollfus, 2005 RCT, DB	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)

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

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Davidson, 2007 Randomized, DB, PCT, Multicenter, Parallel-group study, 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. Clincal lab evaluations, ECG, vital signs, physicial 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 15% = 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 olazapine groups). Glucose related AE's across all groups = n = 6 SAS = no statistically significant increase
Dollfus, 2005 RCT, DB	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

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Davidson, 2007 Randomized, DB, PCT, Multicenter, Parallel-group study, 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. Movement disorder-related TEAEs = mild or moderate	n=365/n=23	
Dollfus, 2005 RCT, DB		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**	EPS: For measures of EPS, data for only 12 olanzapine and 9 risperidone available AIMS, BAS, and SAS NS difference, small changes	Overall 20 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
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)	No antipsychotics 1 month prior to hospitalization	Anticholergenic 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
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 RCT, DB Inpatients for 1st week then outpatients (companion to Zhong 2006)	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

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
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 databse. 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 (eg, ADHD). Beta-blockers were excluded from the analysis except for propanolol.	see above	see above	see above
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 RCT, DB Inpatients for 1st week then outpatients (companion to Zhong 2006)	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

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
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 olzanzapine 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 attempers (ATs) and nonattempters (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
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 RCT, DB Inpatients for 1st week then outpatients (companion to Zhong 2006)	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

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

Author, year study design	Method of adverse effects assessment	Adverse effects reported
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 Cholestrol: +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
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 RCT, DB Inpatients for 1st week then outpatients (companion to Zhong 2006)	NR	NR

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
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	
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 RCT, DB Inpatients for 1st week then outpatients (companion to Zhong 2006)	NR	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

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
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT Multi-site; 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
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT Multi-site; 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
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT Multi-site; 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 timepoint (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 Bonferonni adjustment. Stratification by improvements of 0.5 or 1.0 SD : NS difference btwn 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
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT Multi-site; 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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Harvey, 2003a (Harvey, 2002a; Harvey, 2002b; Harvey, 2002c all = Sub-analysis of Jeste, 2003) RCT Multi-site; 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
Huang, 2005 Randomized, 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
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT - open label, masked ratings Multi-site - 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 montoring, 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

Huang, 2005
Randomized, 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;
			meanHDL=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

InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT - open label, masked ratings Multi-site - 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 asssessed 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. Occurance 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 mths 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
Huang, 2005 Randomized, 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) andLDL/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
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT - open label, masked ratings Multi-site - 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 antisuicidal 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 mths, 2-3 lifetime suicide attempts, no hx alcohol abuse, smokers, high ISST, Cov-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
Huang, 2005 Randomized, blinding - NR Taiwan- inpatients	NA	NA
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT - open label, masked ratings Multi-site - 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 hypotensin, syncope, dysarthria, consitpation, 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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Huang, 2005 Randomized, blinding - NR Taiwan- inpatients	NR	NR/NR	
InterSePT; Meltzer, 2003 Potkin, 2003a Meltzer, 1996 RCT - open label, masked ratings Multi-site - 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/nonsuccessful) 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 Open-label RCT 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 Open-label RCT 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 Open-label RCT with economic analysis	235/none reported/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 sgnifcantly decraased 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 Funciton:** 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 Open-label RCT 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 mths (p =0.0007) S-A EPS SS time effect; lower scores from baseline to 12 mths (p<0.0001) GBAS: SS decrease in ratings baseline to 12 mths (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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Jerrel, 2002 Open-label RCT 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 mths (p =0.0007) S-A EPS SS time effect; lower scores from baseline to 12 mths (p<0.0001) GBAS: SS decrease in ratings baseline to 12 mths (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, 2007 randomized, double-blind, placebo and active-controlled, multicenter study Europe and India	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
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); thereafeter a fixed dosed based on investigator's judgment	none	antidepressants, except fluvoxamine and lithium. Acute usage of valproic acid, carbamazepine, antiemetics, and steriods. 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
Kane, 2007 randomized, double-blind, placebo and active-controlled, multicenter study 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	630 sreened and randomized
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
Kane, 2007 randomized, double-blind, placebo and active-controlled, multicenter study Europe and India	215/7/500	Placebo - paleperidone6 - paliperidone6 - 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 theCGI-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%
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 sigifnicant difference between any of the tx 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 signficinatly 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 improvment: 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 a R improved on all domains (all p<0.05) except verbal fluency. Normative neurocognitve 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 n MADRS or HAMA-No statistical differences between any tx 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

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Author, year study design	Method of adverse effects assessment	Adverse effects reported
Kane, 2007 randomized, double-blind, placebo and active-controlled, multicenter study 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. Clincal lab evaluations, ECG, vital signs, physicial 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)

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 significnalty 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, agitiation, (each p= NS) Consitpation: 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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Kane, 2007 randomized, double-blind, placebo and active-controlled, multicenter study 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	withdrawals 215 due to AEs 38	
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%) Haldolperidol: 14 (14.4%)	After ~52 weeks of enrollment, the haldolperidol 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% Hgroup 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 hospitalised or required medical intervention for an acute exacerbation of psychosis and had experienced an additional acute exacerbation during the previous 2 years.	long-actingrisperidone (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	NR
Kelly, 2005 RCT, DB Thyroid results from Conley 2003 (different from the Conley 2003 above)	treatment-resistant schizophrenia, 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
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

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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
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 (randomisation), weeks 5, 9, 13, 25, 37 and 53 and at end-point	Mean age: 35 years 43% Male 97% caucasian	Age at diagnosis 26.5	693/629/618
Kelly, 2005 RCT, DB 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
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

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Keks, 2007 RCT	at one year 200/NR/ short-term 378 and long-term 362	Risperidone vs. olanzapine Short-term mean (sd) 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 (sd) and LSM of the difference (95% CI) PANSS Total change at endpoint -6.8 (5.8) vs. -6.5 (6.9) and 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 RCT, DB 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
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	18*/ NR/ 28 *4-risperidone (31%); 5 on quetiapine (42%) and 9 on fluphenzine (69%)	Sexual Dysfucntion: 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)

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 RCT, DB Thyroid results from Conley 2003 (different from the Conley 2003 above)	NR	NR
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%), ammenorrhea: 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 ammenorrhea regained menstruation during Q treatment All cases of gynecomastia resolved during treatment 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.

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Keks, 2007 RCT	Extrapyramidal disorder risperidone 7% vs olanzapine 4%	200 total withdrawals 19 due to Aes	
Kelly, 2005 RCT, DB	NR	NR	
Thyroid results from Conley 2003 (different from the Conley 2003 above)			
Kelly, 2006 R, DB, parallel-group SC, treatment-resistant schizophrenia	NR	7/NR	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

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
Kern, 2006 Open-label randomized trial	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
Kinon, 2006b RCT DB USA (Journal of Clinical Psychopharmacology)	Ooutpatients; DSM IV schizophrenia or schizoaffective disorder; met criteria for prominent negative symptoms, defined as a Positive and Negative Syndrome Scale (PANSS) score $\geq$ 4 (moderate) on at least 3, or $\geq$ 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
Kern, 2006 Open-label randomized trial	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
Kinon, 2006b RCT DB USA (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
Kern, 2006 Open-label randomized trial	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)
Kinon, 2006b RCT DB USA (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
Kern, 2006 Open-label randomized trial	NR	NR
Kinon, 2006b RCT DB USA (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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Kern, 2006 Open-label randomized trial	NR	Total withdrawals 146 Due to Aes 46	Withrawals (53%) from the olanzapine group and (62%) from the aripiprazole group
Kinon, 2006b RCT DB USA (Journal of Clinical Psychopharmacology)	The treatment groups did not differ significantly data=NR	Withdrawals 190 due to Aes 96	

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 RCT, DB 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
Klieser, 1991 Heinrich, 1994 Klieser, 1995 RCT, DB 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

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 RCT, DB 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
Klieser, 1991 Heinrich, 1994 Klieser, 1995 RCT, DB 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 pyhsical 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

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Kinon, 2006a RCT, DB 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 weks (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
Klieser, 1991 Heinrich, 1994 Klieser, 1995 RCT, DB Inpatients	31/3/28	Clinical Global Impression at Enpoint (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

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 RCT, DB 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
Klieser, 1991 Heinrich, 1994 Klieser, 1995 RCT, DB 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%

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Kinon, 2006a	olanzapine vs. ziprasidone	Total withdrawals: 247 (62.7%)	
RCT, DB	SAS (mean change from baseline): -0.37 vs. -0.03, P=0.037	olanzapine: 112 (55.4%)	
Multicenter (40 US centers)	AIMS: -0.68 vs. -0.34, P=0.001	ziprasidone: 135 (70.3%)	
	Barnes Akathisia Scale: -0.12 vs. -0.12, P=0.431		
	Adjunctive use of anticholinergic agents: 18.8% vs. 21.6%, P=0.530	Withdrawals due to AEs: NR	
Klieser, 1991 Heinrich, 1994 Klieser, 1995 RCT, DB 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; 7	

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 R, 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 psychoic 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 R, 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	NR	Patients Reporting Sexual Dysfunction at Endpoint: Q: 4/25(16%) vs R: 12/24(50%); p=0.006
Inpatients and outpatients		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 R, 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 R, 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 organsm: 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 organsm: 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 olazapine 10mg/day and other risperidone 6mg/day)

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Knegtering, 2004 open-label Inpatients and outpatients	NR	NR	
Knegtering, 2006 R, 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 R, DB, parallel, MC Inpatients with persistent June 1999-November 2004, USA	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 chlopromazine 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 R, DB, parallel, MC Inpatients with persistent June 1999-November 2004, USA	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 R, DB, parallel, MC Inpatients with persistent June 1999-November 2004, USA	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)

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Author, year study design	Method of adverse effects assessment	Adverse effects reported
Krakowski, 2006 R, DB, parallel, MC Inpatients with persistent June 1999-November 2004, USA	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"

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Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Krakowski, 2006 R, DB, parallel, MC Inpatients with persistent June 1999-November 2004, USA	"No differences in …. and EPS among the 3 medication groups"	40/8 (C 3; O 1; H 4)	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.

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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.

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

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)

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 Hypersonmia: 104(31%) vs 103(31%) vs 96(28%) vs 74(28%) vs 45(24%), p=0.18 Utrinary 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

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

Author, year study design	EPS	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	

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 2 of 3 (for results and AEs)				
Lieberman, 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.				

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 2 of 3 (for results and AEs)				
Lieberman, 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.				

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 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
Lieberman, 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.		Patients's 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)

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 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 hemosglobin, %: 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 -tryglycerides, 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
Lieberman, 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.		

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Lieberman, 2005 (CATIE Study) Row 2 of 3 (for results and AEs)			
Lieberman, 2005 (CATIE Study) Row 3 of 3 (for results only) Funding: NIHM grant, Foundation of Hope of Raleigh, N.C.			

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Author, year study design	Eligibility criteria	Interventions (drug, dose, duration)	Wash-out period	Allowed other medications
Lindenmayer, 1998, open-label Inpatients	Treatment-refactory schizophrenia	12 week study Mean dose: clozapine: 363.02 mg/day, risperidone: 8.95 mg/day	NR	Anticholinerics
McEvoy, 2006 CATIE Phase 2E	Discontinuation of previous phase 1 treament 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.

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
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

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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
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)

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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
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 faintneww: 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

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Lindenmayer, 1998, open-label Inpatients	NR	NR; 5	
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	

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
McQuade, 2004 Multicenter, RCT, DB Inpatients	Schizophrenia, in acute relapse, requiring hospitalization, 18 years of age and older, a Positive and Negative Syndrome Scale (PANSS) total score of ≥60 and a score of ≥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
McCue, 2006 Open label RCT USA-inpatients Funding- NR	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 Excluded were 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 judgement 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 stabiliser or anxiolytic could be prescribed

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
McQuade, 2004 Multicenter, RCT, DB Inpatients	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
McCue, 2006 Open label RCT USA-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

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McQuade, 2004 Multicenter, RCT, DB Inpatients	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 Cholestrol 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 aripirazole and olanzapine groups."
McCue, 2006 Open label RCT USA-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 (s.d.) 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 (s.d.) 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)

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Author, year study design	Method of adverse effects assessment	Adverse effects reported
McQuade, 2004 Multicenter, RCT, DB Inpatients	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%
McCue, 2006 Open label RCT USA-inpatients Funding- NR	Physician judgement	proportion of patients reporting side-effects (week 2: P=0.14; week 3: P=0.72; end-point: P=0.49).

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
McQuade, 2004 Multicenter, RCT, DB Inpatients	EPS-Related Adverse Events: Low: O: 16% vs A: 17% Parkinsonism events: O: 12% vs A: 11% Akathsia: O: 3% vs A: 6%	229 withdrawals; Approx. 30% due to adverse events	
McCue, 2006 Open label RCT USA-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 covariable). Change in score on the Barnes Akathisia Rating Scale from baseline to end-point (F=1.45, d.f.=5,307, P=0.20; age as covariable).	18 withdrawals 14 due to AE	Age was significantly different between groups

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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Mori, 2004	NR	NR	
Inpatients			
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	

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 clinicans 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 R, DB, non-inferiority MC (Germany) Inpatients x 2 weeks and the 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 R, DB, non-inferiority MC (Germany) Inpatients x 2 weeks and the 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, satisfication score; PANSS (including PBRS scores (BPRS0-6), CGI at screening and CGI Improvment 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 R, DB, non-inferiority MC (Germany) Inpatients x 2 weeks and the 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 R, DB, non-inferiority MC (Germany) Inpatients x 2 weeks and the 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 gluc CGI Therapeutic Index: O > C (mean index: Olanazpine: 2.17 ± 1.22, clozapine 1.63 ± 1.14). CGI Therapeutic Effect ratings were similar in both groups CGI Side Effects:no or no significnat 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	EPS	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 psuedo-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 R, DB, non-inferiority MC (Germany) Inpatients x 2 weeks and the 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)	71/12	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 RCT, DB 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 afer 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 hydrocloride (≤8 mg/day)
Potkin, 2003b RCT, DB, placebo-controlled, parallel, multicenter Inpatients	Acute, psychosis in patients diagnosed with schizophrenia and schizoaffective disorder Exclusion criteria: psychiatric disorder other than schizophrena, schizoaffective disorder requiring pharmacotherapy, history of violence, recent history of suicide ideation/attempts, clinically significant neuroloical abnormality other than tardive dyskinesia or EPS, current diagnosis of psychactive 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
Naber, 2005 RCT, DB 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
Potkin, 2003b RCT, DB, 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
Naber, 2005 RCT, DB 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/associality: 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
Potkin, 2003b RCT, DB, 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
Naber, 2005 RCT, DB Inpatients and outpatients	Physical examination	Weight gain: R 1.72 (SD 3.57) kg v Q 2.93 (SD 4.02); p=0.296 Akathisia: R 8 (36.4%) v Q 0; p=0.006 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 Parkinsonism: R 8 (36.4%) v Q 0; p=0.006 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 Use of anticholinergic medication: R 9 (40.9%) v Q 2 (9.1%); p=0.037 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)
Potkin, 2003b RCT, DB, 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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Naber, 2005 RCT, DB Inpatients and outpatients	Olanzapine vs clozapine Simpson Angus Scale Total Mean Change: -2.7 vs -2.1, NS	19/3	
Potkin, 2003b RCT, DB, 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; 44	

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 RCT, DB	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 antipsychoitic 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 mmg/d (>70 kg) on Day 8	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 RCT, DB	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 RCT, DB	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

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 RCT, DB	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%)

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Potkin, 2006 RCT, DB	Monotherapy Phase (resperidone 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 Multicenter, Canada Double-blind RCT	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 Multicenter, Canada Double-blind RCT	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 demential: 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 Multicenter, Canada Double-blind RCT	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 Multicenter, Canada Double-blind RCT	EPS: ESRS, Barnes Akathisia scale, Anti-EPS medications	ESRS: olanzapine/risperidone (p-value) Total score NR Parkisonism: -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%) Dizzines: 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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Purdon, 2000 David, 1999 Jones, 1998 Multicenter, Canada Double-blind RCT	ESRS: olanzapine/risperidone (p-value) Total score NR Parkisonism: -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	Withdrawals due to AE: 48 (8.7%), 9 (5.1%) Total withdrawals: 176 (31.8%), 59 (33.7%)	

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
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.

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
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

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 btwn 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)
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 covarying for BL QOL. All effect Psychological: p=0.100 (NS) Social: p=0.015 Environmental: p=0.643 (NS) Overall QOL: p=0.040 Health Satisfaction p=0.031

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 proformas was used for assessing side effects associated with elevated prolactin and cholinergic antagonism"	EPS SAS and BARS: SS change from baseline (reduction) in both groups NS difference btwn groups AIMS: SS change from baseline in olanzapine group, not in risperidone group; NS difference btwn 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)
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 occuring > 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 signficant differences observed between the two groups"

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

Author, year study design	EPS	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	
Ritchie, 2003 Pragmatic RCT Multicenter, Australia	EPS SAS and BARS: SS change from baseline (reduction) in both groups NS difference btwn groups AIMS: SS change from baseline in olanzapine group, not in risperidone group; NS difference btwn groups	Overall 14 (21%) Due to adverse events: 3 (in risperidone arm = 9%)	Not ITT Only switch data presented, 6-month and 1 year follow-up data to come.
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, nine (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.

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) Multicenter, open label RCT	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.
Sethuraman, 2005 Sub-analysis of Tran 1997	Same as Tran 1997	Same as Tran 1997	Same as Tran 1997	Same as Tran 1997

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) Multicenter, open label RCT	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
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

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) Multicenter, open label RCT	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.
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

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) Multicenter, open label RCT	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)
Sethuraman, 2005 Sub-analysis of Tran 1997	NR	NR

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Sajatovic, 2002 (QUEST sub-group analysis, Mullen, 2001) Multicenter, open label RCT	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.
Sethuraman, 2005 Sub-analysis of Tran 1997	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
Simpson, 2004 multicenter, DB, 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/schizoaffecive 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 reults 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.
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

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, 2004 multicenter, DB, 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
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	NR	NA/NR/1236

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
Simpson, 2004 multicenter, DB, 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 cholestrol: 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 cholestrol: 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
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)

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

Author, year study design	Method of adverse effects assessment	Adverse effects reported
Simpson, 2004 multicenter, DB, 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
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

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Simpson, 2004 multicenter, DB, Parallel, flexible-dose Inpatients	Scales used: Extrapyramidal Symptom Rating Scale, Barnes akathisia scale, Abnormal Involuntary Movement Scale (AIMS)	115; 5	
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)	Total withdrawals 88 due to AE 25	

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
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
Stroup, 2006 CATIE Phase 2T	schizophrenia patients who had just discontinued treatment beacause 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.

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
Sirota, 2006 RCT, DB(?)	Assesment 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
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

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
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
Stroup, 2006 CATIE Phase 2T	395 withdrawn of which 106 were taken out because of changed protocal./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)

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

Author, year study design	Method of adverse effects assessment	Adverse effects reported
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)
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 faintneww: 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

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
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)/ 1 (O - jaundice)	
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	

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, 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
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
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
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
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
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 RvsO 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
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 faintneww: 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
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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
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	
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 interepisode 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 dyskines 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	EPS	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 favour 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 favour 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, schizofreniform, schizoaffective disorder	6-10 week study Median doses: olanzapine: 15 mg/day, risperidone: 4 mg/day	NR	Antidepressants, benzodiazepines, mood stabilizers, anticholinergics

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

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

Author, year study design	Withdrawn/ Lost to fu/ Analyzed	Results
van Bruggen, 2003	NR/NR/31	Mean change in scores from baseline to endpoint: PANSS Total: O: -15.1 vs R: -15.0
Inpatients		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%

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 Associatin 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% Menstral 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%

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

Author, year study design	EPS	Total withdrawals; withdrawals due to adverse events	Comments
van Bruggen, 2003	Parkinsonism: O: 3% vs R: 3%	NR/NR	
Inpatients			

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 RCT, DB 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 hydrocholide, 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 RCT, DB 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 RCT, DB Inpatients	0/0/157 22 analyzed with Total Aggression Severity (TAS) 101 analyzed for glucose and cholestrol 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 cholestrol 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 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 RCT, DB 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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Volavka, 2001 RCT, DB 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;0	

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 compentence 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 difficulites); and adjunctive medications or anti-Parkinsonian medicaitons 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 postrandomization exclusion/85 analyzed	<u>Clinical outcomes at 12 months (olanzapine vs. quetiapine)</u> 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 <u>Functional outcomes at 12 months (olanzapine vs. quetiapine)</u> 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	EPS	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	0/0	
Wahlbeck, 2000 Open-label RCT	NR	Overall: 6/20 ((30%) Due to AE: 3 (15%) 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 chizophrenia 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

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%	Schozophrenia: 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

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--Positve 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) Anxietyand 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)

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 exhitibited 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

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

Author, year study design	EPS	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).	Total withdrawals: 13 (36%) risperidone: 8 olanzapine: 5 Due to AEs: 6 (16.7%) risperidone: 4 olanzapine: 2	

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 ziprazadone 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 diasgnosed 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; specifric 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%	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 <u>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)</u> 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 enpoint using the Simpson-Angus scale for Parkinsonisn 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	EPS	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 swtiching from: Conventional antispychotics: 11% Olanzapine: 6% Risperidone: 9%	
Wu, 2006 Wu, 2007 Randomized, unblinded, longitudinal study	NR	Total withdrawals: 8 Withdrawals due to AEs: 0	

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 perospirione: 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	EPS	Total withdrawals; withdrawals due to adverse events	Comments
Yamashita, 2004 Inpatients	NR	NR	
Zhong, 2004 Poster Only RCT	Risperidone vs quetiapine Spontaneously reported EPS: 21.8% vs 12.7%, P=0.002 EPS-related withdrawals: 3.9% vs 0.29%, P-value NR Abnormal Involuntary Movement Scale Mean Change: -0.25 vs -0.50, NS Simpson-Angus Scale Mean Change: -0.21 vs -0.41, NS Barnes Akathisia Rating Scale: +0.01 vs -0.09, P=0.05	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 p.r.n.. 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 subcale scores; proportion of pts who had ≥ 30% reduction in PANSS total and subcale 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 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 AE : 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 (ngL) 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	EPS	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 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")
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

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, rw 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)
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

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	
Atmaca, 2003 Fair	
Azorin, 2001 Anand, 1998 Double-blind, Multicenter (France and Canada) Fair	
Bai, 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?
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
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

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
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
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

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

Author, year quality rating	Comments
Beasley, 2003 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study Fair	
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	

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
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
Chue, 2005 Fair	NR	NR	No- ILA 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

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.
Chan, 2007 Fair	Yes- only 62 (75%) completed	None	Yes	Fair
Chin, 2006 Fair	None-100% completion	None	Yes	Fair
Chiu, 2006 Fair	Mpme - 100% completion	None	Yes	Fair
Chrzanowski, 2006	Yes, No, No, No	None	LOCF for 211/214 = 98%	Fair
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

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

Author, year quality rating	Comments
Canive, 2006 Poor	
Chan, 2007 Fair	
Chin, 2006 Fair	
Chiu, 2006 Fair	
Chrzanowski, 2006	
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	

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?
Conley, 2005 Fair	Yes	NR	Yes	Yes	NR	NR	NR
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
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
Davidson, 2007 Fair	NR	NR	Yes	Yes	Yes	Yes	Yes
Dollfus, 2005 Poor	Method NR	Method NR	Unclear only provided info regarding age, sex and illness duration	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
Conley, 2005 Fair	Yes	Yes; high and differential RIS 31% QU 42% FLU 64%	Yes	Fair
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	No/ no	No: 91.9%	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
Davidson, 2007 Fair	Yes; completion rate = 59%	No/no	No; exceeded 13/618	Fair
Dollfus, 2005 Poor	NR	NR	Unclear number of pts included in analysis. Endpoint analysis excluded non responders (7%)	Poor

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

Author, year quality rating	Comments
Conley, 2005 Fair	
Covington, 2000 Poor	
Crespo-Facorro, 2006 Fair	
Csernansky, 2002 Fair	
Cutter, 2006 Fair	
Daniel, 1996 Crossover design Poor	
Davidson, 2007 Fair	
Dollfus, 2005 Poor	76/160 planned sample size enrolled. Study not adequately powered.

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?
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
Garyfallos, 2003 CCT Poor	NR	NR	Yes	No	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
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
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
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)

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
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
Garyfallos, 2003 CCT Poor	Yes	No	Yes	Poor
Green, 2002 Marder, 2003 Fair	Attrition yes	Not reported	Yes	Fair
Hamilton, 1998 Fair	Yes	No	Yes	Fair
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
Hertling, 2003 Fair	No	Not reported	No	Fair
Hirsch, 2002 Fair	Attrition yes	NR	No	Fair
Huang, 2005 Poor	NR	LTFU-NR Withdrawal rates NR but 97/126 (77%) completed blood sampling and final assessment of severity	No	Poor

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

Author, year quality rating	Comments
Emsley, 1999 International multicenter (does not include US) Fair	
Garyfallos, 2003 CCT Poor	
Green, 2002 Marder, 2003 Fair	
Hamilton, 1998 Fair	
Harvey, 2003a Harvey, 2002a Harvey, 2002b Harvey, 2002c RCT Multi-site; US, Austria, Israel, Norway, Poland and The Netherlands Fair	
Hertling, 2003 Fair	
Hirsch, 2002 Fair	
Huang, 2005 Poor	Lack of randomization, allocation concealment, blinding along with lack of baseline characteristics or ITT indicate potential for important bias

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?
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, Norway, The Netherlands, Austria) 1 full paper, 2 conference procedures FAIR	Method not reported	Method not reported	Yes	Yes	Yes; method not reported	Yes; method not reported	Yes; method not reported
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

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
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, Norway, The Netherlands, Austria) 1 full paper, 2 conference procedures FAIR	Yes	No; No	Yes	Fair
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

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

Author, year quality rating	Comments
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, Norway, The Netherlands, Austria) 1 full paper, 2 conference procedures FAIR	
Jones, 1998 Purdon, 2000 David, 1999 Multicenter, Canada Double-blind RCT Fair	
Kahn, 2007 RCT, multi-center, international, double-blind, placebo-controlled 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, 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
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
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

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, 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
Kane, 2007 Fair	Attrition-yes	LTFU-NR ~25% total withdrawn Differential: overall low, but there was a 6% difference between aripiprazole and perphenazine for those who discontinued due to AE	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
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

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

Author, year quality rating	Comments
Kane, 2003 Nasrallah, 2004 Fair	
Kane, 2006 Fair	
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
Kasper, 2003 Fair	
Keefe, 2006 OL v RIS v Poor	
Keks, 2007 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?
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
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
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
Knegtering, 2004 Open, single center, parallel Poor	NR	NR	Yes	Yes	No	No	No
Knegtering, 2006 OL v RIS Fair	unclear; open label, says randomized.	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
Kern, 2006 Poor	Yes, no, yes, no	N/N	169/255 = 66% analyzed	Poor
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)
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
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
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

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

Author, year quality rating	Comments
Kern, 2006 Poor	
Kern, 2006 FDA Study 98213 RCT, multicenter, open label Fair	
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	
Knegtering, 2004 Open, single center, parallel Poor	
Knegtering, 2006 OL v RIS 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?
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 antipsych	Yes	Unclear, reported as DB	Unclear, reported as DB	Unclear, reported as DB
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 US and Europe Good	Method NR	NR	Yes	Yes	Yes	Yes	Yes
Lieberman, 2005 (CATIE Study) Good	Yes	Yes, "done under double blind conditions"	Few minor differences	Yes	Yes	Yes	Yes
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
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
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

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
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
Lee, 1999 Fair	Attrition yes	No	No	Fair
Liberman, 2002 Poor	NR	NR	NR	Poor
Lieberman, 2003 US and Europe Good	No/No/No/No	NR	Yes	Good
Lieberman, 2005 (CATIE Study) Good	Yes (74%)	Yes Yes	Yes	Good
Lieberman, 2003 Green, 2004 Fair	Attrition yes	Not reported	No	Fair
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
Luthringer, 2007 Fair	Attrition-14%	No/No	Unclear for PANSS, but assume No, as with sleep outcomes	Fair

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

Author, year quality rating	Comments
Krakowski, 2006 CLO v OL v HOL Fair	
Kramer, 2007 Study was terminated early Fair	
Lee, 1999 Fair	
Liberman, 2002 Poor	
Lieberman, 2003 US and Europe Good	
Lieberman, 2005 (CATIE Study) Good	
Lieberman, 2003 Green, 2004 Fair	
Lindenmayer, 1998 Open-label Pragmatic trial Poor	
Luthringer, 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?
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
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
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

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
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
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
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

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

Author, year quality rating	Comments
Malla, 2004 Canada Poor	
Marder, 2007 Good	
McCue, 2006 Fair	
McEvoy, 2007 Fair	
McEvoy, 2007 Good	
McQuade, 2004 RCT, multicenter, double-blind Fair	
Naber, 2001 Poor	
Naber, 2005 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?
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
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
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
QUEST; Mullen, 2001 Mullen, 1999 Reinstein, 1999 Fair	Method not reported	Method not reported	Yes	Yes	No	No	No
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

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
Nicolai-Costa, 2007 Poor	Attrition-yes (~14%); No patient changed their allocated group	LTFU-low (1-patient) 14% total withdrawn Differential: NR	NR	Poor
Peuskens 2007 Fair	Yes	Yes/No. Withdrawal rate was 67% compared to 17% in treatment group.	Yes	Fair
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
QUEST; Mullen, 2001 Mullen, 1999 Reinstein, 1999 Fair	No	NR	Yes, using LOCF	Fair
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

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

Author, year quality rating	Comments
Nicolai-Costa, 2007 Poor	
Peuskens 2007 Fair	
Peuskens, 1999 Fair	
Potkin, 2003 Fair	
Potkin, 2006 Good	
QUEST; Mullen, 2001 Mullen, 1999 Reinstein, 1999 Fair	
Riedel, 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?
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
Sayers, 2005 Fair-Poor	Method not reported	Yes	Unclear; only age, smoking and cocaine use given	Yes	Yes	Not reported	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

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
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
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
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

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

Author, year quality rating	Comments
Ritchie, 2003, 2000 Pragmatic RCT Multicenter, Australia Fair	
Robinson, 2006 Fair	
Rosenheck, 1997 Fair	
Rosenheck, 2003 Fair	
Rubio, 2006 Poor	
Sayers, 2005 Fair-Poor	
Schooler, 2005 Fair	
Sechter, 2002 Fair	
Shopsin, 1979 Fair	
Shrivastava, 2000 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?
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
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

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
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
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

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

Author, year quality rating	Comments
Silva de Lima, 2005 Fair	
Simpson, 2004 Fair	
Sirota, 2006 Fair	
Smelson, 2006 Fair	
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	

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?
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
Tunis 2006 Fair	Method not reported	Method not reported	Yes	Yes	No	No	No
Tran, 1997 Fair	Method not reported	Method not reported	Unclear - not well reported	Yes	NR	Yes	Yes
Tran-Johnson, 2007 Fair	Method not reported	Method not reported	Yes	Yes	NR	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
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
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

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
Tollefson, 2001 Beasley, 1999 Beuzen, 1998 Fair	Yes	No	Yes (LOCF methods)	Fair
Tunis 2006 Fair	Yes	No/No	Yes	Fair
Tran, 1997 Fair	Yes	Overall 47.5% olanzapine 57.6% risperidone 47.3%	Yes	Fair
Tran-Johnson, 2007 Fair	Yes	No/no	Yes (LOCF)	Fair
van Bruggen, 2003 Poor	NR	Yes- 2/26 risperidone vs 0/18 olanzapine not included in analysis	No: 2 risperidone patients excluded	Poor
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
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) Ris vs. 29% (5) Olan [study states these were similar, no statistics reported]	Yes, using LOCF	Fair

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

Author, year quality rating	Comments
Tollefson, 2001 Beasley, 1999 Beuzen, 1998 Fair	
Tunis 2006 Fair	
Tran, 1997 Fair	
Tran-Johnson, 2007 Fair	
van Bruggen, 2003 Poor	
Vanelle, 2006 Good	
Velligan, 2003 Fair	
Voruganti, 2007 Fair	
Wahlbeck, 2000 Open-label RCT Fair	
Wang, 2006 RCT, double-blind Fair	Small number of patients.

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?
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

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
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

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

Author, year quality rating	Comments
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	

Evidence Table 3. RCTs 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 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, shizoaffective disorder, brief reactive psychosis, schizotypal personality disorder or physchosis 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. RCTs 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 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. RCTs 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	Outcome scales
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	PANSS, CDSS, BAS, AIMS
Crespo-Facorro, 2006 Spain	No previous antipsychotic treatment: 98.3% Inpatient: 63.4%	202/182/182	10 withdrawn after randomization 172 analyzed	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)

Evidence Table 3. RCTs in patients with first episode schizophrenia

Author, year Country Trial Name	Method of outcome assessment and timing of assessment
Apiquian, 2003 Mexico Mexican First-Episode Psychotic Study	PANSS; CDSS,;AIMS; Barnes akathasia scale at baseline, 3 months and 6 months
Crespo-Facorro, 2006 Spain	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. RCTs 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 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 Clinical response rate (>/= 40% BPRS total improvement from baseline: haloperidol: 57.1% risperidone: 52.5% olanzapine: 63.6% Mean time to response (SD): haloperidol: 4.32 weeks (0.24) risperidone: 4.85 weeks (0.21) olanzapine: 4.36 weeks (0.23)

Evidence Table 3. RCTs 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 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. RCTs 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. RCTs 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. RCTs 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	Outcome scales
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	PANSS, BPRS;Extrapyramidal Symptom Rating Scale
Green, 2004 Sub-analysis of Lieberman 2003: Effects of comorbid substance abuse	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003

Evidence Table 3. RCTs in patients with first episode schizophrenia

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

Evidence Table 3. RCTs 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. RCTs 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. RCTs 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 years	Same as Lieberman 2003	Same as Lieberman 2003	Same as Lieberman 2003

Evidence Table 3. RCTs 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

Evidence Table 3. RCTs 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	Outcome scales
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)	Same as Lieberman 2003

Evidence Table 3. RCTs in patients with first episode schizophrenia

Author, year Country Trial Name	Method of outcome assessment and timing of assessment
Green, 2006 Companion to Lieberman, 2003: Two-year data	Same as Lieberman 2003

Evidence Table 3. RCTs 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)

Evidence Table 3. RCTs 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.

Evidence Table 3. RCTs 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 Halperidol 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. RCTs 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 (benzotropine, biperiden, propanolol, procyclindine)	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 nefazadone) and anti-anxiety medications (lorzepam 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. RCTs 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	Outcome scales
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	PANSS; CGI Severity; Montgomery-Asberg Depression Rating Scale
Malla, 2004 Canada	Mean age at diagnosis: 21.6 yrs	NR/NR/84	52/NR/32	SANS

Evidence Table 3. RCTs in patients with first episode schizophrenia

Author, year Country Trial Name	Method of outcome assessment and timing of assessment
Lieberman, 2003 Zipursky, 2005 (time to weight gain results) US & Europe HGDH Research Group	Weekly physician-assessments wks 1-6, biweekly wks 7-12
Malla, 2004 Canada	baseline, 1 year physician assessments

Evidence Table 3. RCTs 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. RCTs 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. RCTs in patients with first episode schizophrenia

Author, year Country Trial Name	N	Duration	Study design Setting	Eligibility criteria	Interventions (drug, dose, duration)
McEvoy, 2006 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. RCTs in patients with first episode schizophrenia

Author, year Country Trial Name	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
McEvoy, 2006 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. RCTs 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	Outcome scales
McEvoy, 2006 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	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
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	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.

Evidence Table 3. RCTs in patients with first episode schizophrenia

Author, year Country Trial Name	Method of outcome assessment and timing of assessment
McEvoy, 2006 USA CAFE: Comparison of Atypicals in First Episode of Psychosis	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	Baseline and every week for the first 4 weeks, then every 2 weeks

Evidence Table 3. RCTs in patients with first episode schizophrenia

Author, year Country Trial Name	Results
McEvoy, 2006 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%
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. RCTs in patients with first episode schizophrenia

Author, year Country Trial Name	Adverse events	EPS	Comments
McEvoy, 2006 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 irregularitiesb 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. RCTs 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 years	Double blind RCT	16–45 year-old Structured Clinical Interview for DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder < 1 year; nomore 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 Liberman 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

Evidence Table 3. RCTs 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

Evidence Table 3. RCTs 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	Outcome scales
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	PANSS; CGI Severity; EPS rating scale
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	SF-36

Evidence Table 3. RCTs in patients with first episode schizophrenia

Author, year Country Trial Name	Method of outcome assessment and timing of assessment
Schooler, 2005 Multi-national	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	Planned physician assessements at baseline and at 3 mos, 6 mos and 1 year. Included patients had baseline and at least one additional assessment

Evidence Table 3. RCTs in patients with first episode schizophrenia

Author, year Country Trial Name	Results
Schooler, 2005 Multi-national	Risperidone vs. haloprido 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

Evidence Table 3. RCTs 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. halopridol Dyskinesia Baseline 1.1% vs 1.4% Emergent 8.3% vs. 13.4% Persistant 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	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Andrezina, 2006 US, Czech Republic, France, Estonia, Latvia, Poland, Croatia, Italy, Puerto Rico, South Africa, and Spain	haloperidol	IM aripiprazole 9.75 mg, IM haloperidol 6.5 mg, or IM placebo Duration: 24 hours	NA/NA	Mean improvement in PEC (five items on the PANSS total scale (hostility, lack of cooperation, excitement, poor impulse control, and tension) at 2 hours
Avasthi, 2001 India	haloperidol	olanzapine 5-20 mg/day haloperidol 5-20 mg/day Duration: 12 weeks	NR/ NR	Primary efficacy measure: BPRS, PANSS, Scale for the Assessment of Negative Symptoms (SANS), Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton-Anxiety Scale (HAM-A), CGI, Quality of Life Scale (QOL)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Andrezina, 2006 US, Czech Republic, France, Estonia, Latvia, Poland, Croatia, Italy, Puerto Rico, South Africa, and Spain	At 2 hours after injection PEC change from baseline IM aripiprazole (−7.27) vs placebo (−4.78) p<0.001 and IM haloperidol -7.75 (p = NS) CGI-I placebo 3.10 vs. aripiprazole 2.42** vs. haloperidol 2.37** Change in CGI-S Placebo −0.71 vs. aripiprazole −1.16** vs. haloperidol −1.17** *p≤0.05 vs placebo **p≤0.01 vs placebo
Avasthi, 2001 India	Baseline vs endpoint, p vs baseline olanzapine: BPRS- total: 23.31(9.94) vs 9.50(7.06), p<0.01 BPRS- positive: 9.12(5.35) vs 3.75(4.25), p<0.01 BPRS- negative: 5.06(4.14) vs 3.12(3.42), p<0.01 BPRS- anxiety: 4.19(2.20) vs 1.31(1.66), p<0.01 PANSS- positive: 19.37(7.06) vs 11.44(4.11), p<0.01 PANSS- negative: 21.87(7.69) vs 15.62(7.93), p<0.01 PANSS- GenPsyPath: 36.56(9.46) vs 25.12(5.25), p<0.01 MADRS: 9.12(5.15) vs 3.00(2.42), p<0.01 HAM-A: 8.31(5.13) vs 2.31(2.47), p<0.01 CGI-severity: 4.68(0.89) vs 3.19(0.98), p<0.01 SANS total score: 32.94(19.69) vs 21.87(19.47), p<0.05 QOL: 47.0(24.64) vs 51.19(23.38), NS haloperidol: BPRS- total: 25(4.56) vs 12.57(13.39), p<0.05 BPRS- positive: 7.43(5.53) vs 3(5.51), p<0.05 BPRS- negative: 5.29(2.50) vs 3.57(2.37), NS BPRS- anxiety: 4.86(2.34) vs 2.71(2.87), NS PANSS- positive: 19.29(10.86) vs 10.86(8.49), p<0.05 PANSS- negative: 23.29(8.37) vs 16.86(8.71), p<0.05 PANSS- GenPsyPath: 38.29(9.45) vs 26.57(8.73), p<0.05 MADRS: 10.29(4.61) vs 5(4.58), NS HAM-A: 9.71(3.8) vs 4.57(4.72), NS CGI-severity: 4.29(1.11) vs 2.86(1.57), p<0.05 SANS total score: 39.71(12.05) vs 27.43(19.48), NS QOL: 38.29(31.74) vs 49.14(33.88), NS

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Andrezina, 2006 US, Czech Republic, France, Estonia, Latvia, Poland, Croatia, Italy, Puerto Rico, South Africa, and Spain	Patient and investigator reported; EPS via SAS and BAS; lab tests included standard and ambulaory 12 lead ECGs and vital signs	IM placebo vs. vs. IM aripiprazole vs. IM haloperidol n(%) Headache 6 (6.9) vs. 13 (7.4) vs. 15 (8.2) Dizziness 2 (2.3) vs. 11 (6.3) vs. 7 (3.8) Nausea 1 (1.2) vs. 10 (5.7) vs. 2 (1.1) Insomnia 8 (9.2) vs. 10 (5.7) vs. 22 (12.0) Agitation 5 (5.8) vs. 7 (4.0) vs. 8 (4.4) Extrapyramidal disorder 0 vs. 1 (0.6) vs. 10 (5.5)
Avasthi, 2001 India	UKU side Effect Rating Scale Simpson Angus Scale Barnes Akathisia Rating Scale	Baseline vs endpoint, p vs baseline olanzapine: Barnes akathisia: 0.44(1.09) vs 0(0), NS Simpson-Angus: 1.37(7.71) vs 0.75(1.39), NS haloperidol: Barnes akathisia: 0.43(0.79) vs 0.29(0.49), NS Simpson-Angus: 1.43(2.57) vs 0.86(1.86), NS Emergent side-effect, N(%) olanzapine vs haloperidol asthesnia: 7(43.7%) vs 3(42.9%) sleepiness: 8(50%) vs 2(28.6%) tension: 0(0%) vs 4(57.1%) increased duration of sleep: 7(43.7%) vs 2(28.6%) dystonia: 0(0%) vs 1(14.3%) rigidity: 1(6.2%) vs 5(71.4%) hypokinesia: 1(6.2%) vs 2(28.6%) tremor: 5(31.2%) vs 4(57.1%) akathesia: 1(6.2%) vs 2(28.6%) accomodation disturbance: 0(0%) vs 2(28.6%) increased salivation: 3(18.7%) vs 0(0%) reduced salivation: 4(25%) vs 0(0%) constipation: 5(31.2%) vs 0(0%) micturition disturbances: 1(6.2%) vs 2(28.6%) weight gain: 13(81.2%) vs 2(28.6%) others: 5(31.2%) vs 7(100%) *Others: polyuria, orthostatic dizziness, papitations, nausea, increased sweating and menstrual disturbances.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Andrezina, 2006 US, Czech Republic, France, Estonia, Latvia, Poland, Croatia, Italy, Puerto Rico, South Africa, and Spain	13 withdrawals 3 due to AE	
Avasthi, 2001 India	NR	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Barak, 2002 Israel	haloperidol	Mean dosage at the end olanzapine 13.1(5.9) mg/day, range 5.0-25.0 haloperidol 7.2(2.9) mg/day range NR mean duration: 15(8) month, range 3-24	NR	Primary outcome: PANSS and CGI

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Barak, 2002 Israel	Baseline vs posttreatment PANSS total: haloperidol: 79.3(15.3) vs 74.3(9.6) olanzapine: 84.0(14.5) vs 65.1(19.3) *change from baseline, haloperidal vs olanzapine, p=0.02 PANSS negative: haloperidol: 18.2(7.9) vs 20.5(6.9) olanzapine: 18.9(3.4) vs 15.2(3.0) *change from baseline, haloperidal vs olanzapine, p=0.0003 PANSS general: haloperidol: 40.9(12.3) vs 36.5(7.0) olanzapine: 40.7(9.0) vs 34.5(10.6) PANSS positive: haloperidol: 20.2(7.3) vs 17.3(6.1) olanzapine: 24.4(8.0) vs 15.4(7.8) CGI haloperidol: 4.8(0.9) vs 4.4(0.5) olanzapine: 4.9(1.2) vs 3.8(0.9)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Barak, 2002 Israel	weight, blood pressure and pulse	olanzapine (n=10) vs haloperidol (n=10) weight: 4.5(0.6) vs 2.1(1.8), p=0.3 blood pressure: NR, NS pulse: NR, NS concomitant psychotropic medication use: 3 vs 7

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Barak, 2002 Israel	olanzapine vs haloperidol total withdrawal: 4 vs 4 withdrawal due to AEs: 0 vs 3 * the three patients discontinued from the haloperidol group were treated with higher doses compared to other 7 patients (9.0 vs 5.4)	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Beasley, 1997 Europe, South Africa, Israel, Australia	haloperidol benzodiazepine: lorazepam equivalents maximum dose of 10 mg/day	olanzapine 1mg/day olanzapine 5(2.5) mg/day olanzapine 10(2.5) mg/day olanzapine 15(2.5) mg/day haloperidol 15(5.0) mg/day Duration: 6 weeks acute phase followed buy a 46 weeks extension phase for responders to acute phase. The acute-phase results are reported here.	4-7 days/2 days	BPRS extracted from the PANSS PANSS CGI Severity Patient Global Impression (PGI)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Beasley, 1997 Europe, South Africa, Israel, Australia	olz-1 vs olz-5 vs olz-10 vs olz-15 vs hal-15 Endpoint change from baseline, Mean(SD) BPRS total: -10.5(16.6) vs -13.4(14.8) vs -13.8(17.8) vs -16.4(14.3) vs -12.4(16.0) BPRS positive: -3.1(4.9) vs -4.5(4.6)* vs -4.3(5.3) vs -5.3(4.6)* vs -4.8(5.1) BPRS negative: -2.1(3.5) vs -2.4(3.4) vs -2.3(3.6) vs -2.8(3.0) vs -1.9(2.9) PANSS total: -16.8(28.7) vs -21.4(25.2) vs -22.7(29.2) vs -26.7(23.7) vs -20.0(25.9) PANSS positive: -4.3(8.3) vs -6.7(6.7) vs -6.2(8.5) vs -8.2(7.4)* vs -6.5(8.6) PANSS negative: -4.4(8.2) vs -5.1(7.5) vs -5.4(8.0) vs -6.6(6.9) vs -4.8(6.3) PANSS G psych: -8.2(14.6) vs -9.7(14.4) vs -11.1(15.2) vs -11.9(12.1) vs -8.7(13.4) CGI Severity: -0.8(1.4) vs -1.0(1.1) vs -1.2(1.2) vs -1.5(1.5)* vs -1.1(1.3) -All p<0.001 compared to baseline. *p<0.05 compared with olz-1

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Beasley, 1997 Europe, South Africa, Israel, Australia	EPS assessment: -Simpson-Angus Scale -Barnes Akathisia Scale Dyskinesias: -Assessment of Involuntary Movement Scale (AIMS)	olz-1 vs olz-5 vs olz-10 vs olz-15 vs hal-15 (%), p value Increased ALT: 3.4 vs 6.9 vs 9.3a vs 14.6bc vs 1.2, p=0.007 Headache: 10.2 vs 2.3f vs 9.3 vs 9.0 vs 7.4, p=0.296 EPS: 2.3 vs 2.3c vs 1.2c vs 5.6 vs 13.6b, p=0.001 Insomnia: 11.4 vs 6.9 vs 4.7 vs 5.6 vs 2.5f, p=0.172 Akathisia: 0.0 vs 0.0d vs 1.2d vs3.4c vs 14.8e, p<0.001 Hypertonia: 0.0 vs 1.1a vs 1.2a vs 1.1a vs 9.9b, p<0.001 Dyskinesia: 1.1 vs 0.0a vs 1.2 vs 0.0a vs 6.2, p=0.009 Dystonia: 0.0 vs 0.0a vs 0.0a vs 0.0a vs 4.9f, p=0.002 Increased GGT: 0.0 vs 4.6f vs 2.3 vs 0.0 vs 0.0, p=0.030 Increased salivation: 0.0 vs 1.1 vs 1.2 vs 0.0a vs 6.2f, p=0.009 Tremor: 0.0 vs 1.1c vs 1.2c vs 0.0d vs 11.1e, p<0.001 a: p≤0.05 compared with Hal b: p≤0.01 compared with Olz-1.0 c: p≤0.01 compared with Hal d: p≤0.001 compared with Hal e: p≤0.001 compared with Olz-1.0 f: p≤0.05 compared with Olz-1.0 -Weight gain was associated with increasing olanzapine dose;a slight decrease in weight was seen in the haloperidol treatment group. olz-1 vs olz-5 vs olz-10 vs olz-15 vs oal-15 (%), p value Simpson-Angus: -0.61(2.95) vs -1.08(3.76)d vs -0.17(3.45)d vs -0.66(3.21)d vs 3.00(8.06)e Barnes: -0.19(0.61) vs -0.20(0.69)d vs -0.18(0.84)d vs -0.07(0.74)d vs 0.47(1.26)b AIMS: -0.71(2.58) vs -0.55(2.44)a vs 0.07(2.02) vs -0.33(2.69) vs 0.15(3.25)c a: p≤0.1 vs Hal b: p≤0.1 vs Olz-1 c: p≤0.5 vs Olz-1 d: p≤0.01 vs Hal e: p≤0.01 vs Olz-1

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Beasley, 1997 Europe, South Africa, Israel, Australia	Olz-1 vs Olz-5 vs Olz-10 vs Olz-15 vs Hal-15 Total withdrawals (%): 45.5 vs 44.8 vs 38.4 vs 38.2 vs 46.9 vs 42.7 Withdrawals due to AEs: 11.4 vs 16.1 vs 7.0 vs 9.0 vs 14.8 vs 11.6	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Bobes, 2003 Spain	Conventional antipsychotics haloperidol was the most frequently prescribed antipsychotic in the control group, with 60(87%) patients having received this drug at some point during hospitalization and 46(66.7%) were receiving it as treatment upon discharge	olanzapine (N=89): 16.4 mg haloperidol (N=69): 15.5mg other antipsychotics: NR	NR/ NR	CGI-S BPRS NOSIE
Bouchard, 1998 (AO) Bouchard, 2000 Canada	Conventional neuroleptics	risperidone mean dose 5.5 mg/day Conventional neuroleptics mean dose 1006 mg/day in chlorpromazine equivalents* (20.12 mg/day in haloperidol equivalents) 12 months *per Bouchard 1998: median dose 551 mg/day in chlorpromazine equivalents	NR/ NR	PANSS at 3, 6, and 12 months Proportion of responders defined by 20% decrease in total PANSS Per Bouchard 1998: also CGI, ESRS, side effects, and medication at 3, 5, and 12 months.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Bobes, 2003 Spain	olanzapine vs conventional antipsychotics at endpoint, p value CGI mean improvement: 2.0(1.2) vs 1.6(1.1), p=0.013 BPRS total: 30.8 vs 23.6, p=0.0003 BPRS positive: 10.5 vs 8.3, p=0.0019 BPRS negative: 4.0 vs 1.9, p<0.0001 BPRS depression: 5.2 vs 4.2, p=0.018 BPRS agitation:10.2 vs 8.8; P=0.007 NOSIE mean improvement: 20.6 vs 16.9, p=0.0671 *p value adjusted for baseline and duration of course of illness Treatment response rate: 76.7% vs 54.4%, p=0.003 Treatment response rate after adjusting for baseline and time elapsed, p=0.044 BPRS >40% reduction: 73(84.9%) vs 46(67.6%) BPRS 60% reduction: 69.8% vs 45.6%, p=0.001 BPRS 80% reduction: 34.9% vs 19.1%, p=0.001
Bouchard, 1998 (AO) Bouchard, 2000 Canada	Mean change in PANSS score at 12 months (LOCF), risperidone vs typical APs: Total -9.8 vs -3.2 (p=0.005) Positive subscale -2.9 vs -0.9 (p=0.008) Negative subscale -2.6 vs -0.7 (p=0.020) General psychopathology subscale -4.5 vs -1.4 (p=0.015) 20% improvement at 12 months achieved by 29% vs 16% (p=0.04) 30% improvement at 12 months achieved by 17% vs 6% (p=0.02) Per Bouchard 1998: Proportion of patients who achieved >=20% reduction in PANSS score, risperidone vs classical neuroleptics: 30% vs 15% (p=0.027).

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Bobes, 2003 Spain	UKU side effect rating scale	olanzapine vs conventional antipsychotics EPS: 12(13.6%) vs 38(55.9%), p<0.001 Dystonia: 0(0%) vs 10(14.7%), p<0.001 Rigidity: 5(5.7%) vs 12(17.6%), p=0.021 Hypokinesia: 3(3.4%) vs 22(32.4%), p<0.001 Tremor: 3(3.4%) vs 17(25%), p<0.001 Akathisia: 3(3.4%) vs 17(25%), p<0.001 Dyskinesia: 1(1.1%) vs 2(2.9%), p=0.581 Others: 2(2.3%) vs 2(2.9%), p=1
Bouchard, 1998 (AO) Bouchard, 2000 Canada	ESRS, use of antiparkinsonians	% of subjects whose symptoms were worse at 12 months on ESRS subscales, risperidone vs typical APs: Dyskinesia 18.4 vs 20.8% (ns) Parkinson symptoms 14.9 vs 26% (ns) Akathisia 8.1 vs 22.1% (p=0.02)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Bobes, 2003 Spain	A total of 17 patients (11.3%) discontinued ; 11.2% were olanzapine patients (n=10) and 10.1% were conventional patients (n=7)	1/89 clozapine patients was switched to the conventional antipsychotic group; 13/69 in the conventional group were switched to olanzapine (10 were switched due to secondary effects and 3 were insufficient efficacy)
Bouchard, 1998 (AO) Bouchard, 2000 Canada	19 total; due to AEs not reported	Study included only stabilized and severely ill patients with chronic schizophrenia who were already known to be only partially response to typical APs. One treatment arm was open-label medication with current neuroleptic.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Breier, 2002 Croatia, Italy, Romania, South Africa	haloperidol	IM olanzapine 2.5mg (mean: 4.0) IM olanzapine 5.0mg (mean:6.9) IM olanzapine 7.5mg (mean: 9.8) IM olanzapine 10mg (mean:12.6) IM haloperidol 7.5mg (mean 9.9) IM placebo (mean: n/a) 24-hour study, with a maximum of three injections allowed during this time % of pts receiving ≥2 injections over 24h: (p<0.001 for all vs placebo) olz 2.5: 52.1% olz 5.0: 35.5% olz 7.5: 28.3% olz 10.0: 23.9% (p<0.05 vs olz 2.5) hal 7.5: 25% (p<0.05 vs olz 2.5) placebo: 66.7%	NR/ min 2 hour washout in screening period	Primary efficacy measure: PANSS-EC Other measures: Agitated Behavior Scale (ABS), Agitation Calmnes Evaluation (ACES), PANSS-derived Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions-Severity (CGI-S) Pts assessed at screening visit, 30, 60, 90 minutes and 2, 4, 6, 12, and 24 hours after first injection

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Breier, 2002 Croatia, Italy, Romania, South Africa	Change from baseline- Mean (SD), p vs olz 2.5mg, p vs placebo PANSS-EC, 2 hours after IM injection olz 2.5mg: -5.5(4.6), NA, p=0.01 olz 5.0mg: -8.1(5.3), p=0.01, p<0.001 olz 7.5mg: -8.7(5.0), p=0.001, p<0.001 olz 10mg: -9.4(4.9), p<0.001, p<0.001 hal 7.5mg: -7.5(5.9), p=0.04, p<0.001 placebo: -2.9(4.7), p=0.01, NA *other between treatment comparison: p=NS olz 2.5 vs olz 5.0 vs olz 7.5 vs olz 10 vs hal 7.5 vs placebo- Mean(SD) 2 hours after first IM injection BPRS total: -8.2(9.1)e vs -10.4(7.5) vs -12.0(7.0) vs -12.0(5.9) vs -9.2(7.2)b vs -3.7(5.5)a BPRS positive: -1.5(3.1) vs -1.7(2.8) vs -2.1(2.9) vs -1.9(2.3) vs -1.4(2.2) vs -0.4(1.3)a ABS: -5.8(5.5)d vs -9.0(5.5) vs -10.5(5.6)c vs -10.4(5.7)c vs -7.7(5.2)b vs -3.0(5.0)a ACES: 1.3(1.5)d vs 2.3(1.9) vs 2.4(1.7) vs 2.6(1.7)c vs 1.8(1.6)b vs 0.7(1.2)a a: p<0.05 vs all IM olanzapine treatment groups, except olz at 2.5mg on the ACES b: p<0.05 vs placebo c: p<0.05 vs hal d: p<0.05 vs all other olz treatment e: p<0.05 vs olz at 7.5 mg and 10.0mg olz 2.5 vs olz 5.0 vs olz 7.5 vs olz 10 vs hal 7.5 vs placebo- Mean(SD) Mean change from baseline to 24 hours after first IM injection PANSS-EC: -4.9(4.3) vs -5.5(4.9) vs -5.5(4.1) vs -5.9(5.2) vs -4.5(4.0) vs -3.1(3.3)a BPRS total: -8.4(7.4) vs -9.2(7.8) vs -9.6(7.5) vs -9.0(7.7) vs -7.3(7.5) vs -4.3(5.4)a BPRS positive: -1.5(2.3) vs -2.0(2.6) vs -1.9(2.7) vs -1.7(2.4) vs -1.8(3.0)b vs -0.6(2.2)a ABS: -5.7(4.2) vs -6.7(5.9) vs -7.7(5.8)c vs -7.4(7.0)c vs -5.0(4.1)b vs -2.6(4.0)a CGI-S: -0.3(0.5) vs -0.5(0.8)b vs -0.6(0.7)b vs -0.4(0.5) vs -0.4(0.6) vs -0.2(0.6) ACES:+ 0.9(0.8) vs +1.1(1.1) vs +1.0(1.0) vs +0.9(0.9) vs +0.8(0.7) vs +0.5(0.7)a a: p<0.05 vs all IM olanzapine treatment groups, except olz at 2.5mg on the BPRS positive b: p<0.05 vs placebo c: p<0.05 vs hal 7.5mg

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Breier, 2002 Croatia, Italy, Romania, South Africa	Simpson-Angus and Barnes Akathisia Scales	olz 2.5 vs olz 5.0 vs olz 7.5 vs olz 10 vs hal 7.5 vs placebo Hypotension: 4.2% vs 4.4% vs 2.2% vs 4.3% vs 0% vs 0%, (no between group differences observed) Acute dystonia: 0% of all olz (n=185) pts vs 5.0% hal vs 0% placebo pts olz 2.5 vs olz 5.0 vs olz 7.5 vs olz 10 vs hal 7.5 vs placebo Treatment emergent parkinsonism: 0% vs 0% vs 0% vs 2.9% 16.7% vs 0% (p=0.03 for hal vs olz 2.5 and vs olz 5.0; p=0.01 for hal vs olz 7.5 and hal vs placebo) Treatment emergent akathisia: 0% vs 4.8% vs 0% vs 0% vs 7.9% vs 0% (no between group differences observed) Anticholinergic medication given to 7.5% hal pts and 2.1% olz 2.5 pts (no between group differences) No pt had increase in QTc of ≥500 milliseconds Baseline to 24h changes in mean(SD) QTc intervals, "none were clinically relevant" -4.3(22.3) vs -3.1(23.2) vs -2.8(19.6) vs -1.9(31.0) vs +6.5(24.7) vs +1.2(21.5)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Breier, 2002 Croatia, Italy, Romania, South Africa	NA	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Brook, 2000 International	haloperidol	IM treatment: days 1 and through day 3 ziprasidone IM (n=90): initial dose 10 mg; subsequent doses of 5-20 mg given every 4-6 hours (max: 4 injections and 80 mg in 24h) haloperidol IM (n=42): initial dose: 2.5-10 mg; subsequent doses given 4-6 hours (max: 4 injections and 40 mg in 24h) Days 3-7 ziprasidone PO: 80-200 mg/d haloperidol PO: 10-80 mg/d 7 day treatment	NR/ Antipsychotics taken at baseline were discontinued and first dose of IM given when clinically appropriate	BPRS and CGI-S assessed at baseline, once every 24 h while on treatment, and at endpoint CGI-I rated relative to baseline every 24h and at endpoint
Costa, 2007 Brazil	Conventional antipsychotics: 48.5% took haloperidol; 9.1% took chlorpromazine; and 42.4% took a combo of haloperidol and chlorpromazine	Naturalistic dosaging Olanzapine dose ranged from 10-20mg/day, mean dosage was 17.5mg/day Haloperidol dose ranged from 5-20mg/day, mean dosage was 10.5mg/day Chlorpromazine dose ranged from 100-500mg/day, mean dosage was 300mg/day	No	Dickson Glazer Scale for Assessment of Sexual Functioning Inventory (DGSFi) a computerized self-report measure of sexual functioning Blood samples

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Brook, 2000 International	Mean change from baseline score, ziprasidone vs haloperidol: At end of IM treatment: BPRS total: -6.24 vs -3.18, p=0.02 BPRS agitation items: -1.93 vs -0.80, p=0.015 CGI-S: -0.49 vs -0.15, p=0.002 At the endpoint evaluation: BPRS total: -8.76 vs -5.83, p=0.09 BPRS agitation items: -2.09 vs +1.59, p=0.19 CGI-S: -0.89 vs -0.38, p=0.025
Costa, 2007 Brazil	In the conventional treatment group individuals showed and increase in their sex hormone-binding globulin levels. For both groups the prolactin levels were significantly decreased, however for the olanzapine group their prolactin levels decreased significantly more rapidly than the conventional group after 3 months (P=0.01) There was no significant difference between groups on their ratings on the DGSFi

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Brook, 2000 International	AEs classified with COSTART along with investigators' assessments of severity BAS, SARS at baseline, at end of IM treatment, and at endpoint 5-Point sedation scale (1= absent to 5=sleep) rated at baseline and within 6 h of a dose of study medication on days 1-7 or on early termination Lab tests and ECG at baseline, after the last IM dose, and at endpoint	ziprasidone vs haloperidol Change in score (SD) from baseline: SAS at last IM dose: -0.61 (3.11) vs +3.80 (5.22) SAS at endpoint: -1.09 (4.33) vs +6.00 (7.12) BAS at last IM dose: -0.03 (0.57) vs +0.44 (0.87) BAS at endpoint: -0.10 (0.79) vs 0.80 (1.14) Sedation scores at last IM dose: +1.10 (1.56) vs +0.46 (1.17) Sedation scores at endpoint: +0.02 (1.10) vs +0 (0.71) Total % of patients experiencing any incidence of AEs at endpoint: 45.6% vs 59.5% % of patients taking anxiolytics at any time: 57.7% vs 64.3% % of patients taking hypnotics for nighttime sedation: 10% vs 7.1% % of patients taking anticholinergics at any time: 14.4% vs 47.6% % of patients experiencing these adverse events: Tremor (IM only): 1.1% vs 2.4%; (IM+PO): 2.2% vs 9.5% Akathisia (IM only): 2.2% vs 0; (IM+PO): 3.3% vs 14.3% Dystonia (IM only): 1.1% vs 7.1%; (IM+PO): 4.4% vs 11.9% EPS (IM only): 0 vs 21.4%; (IM+PO): 1.1% vs 38.1% Hypertonia (IM only): 0 vs 7.1%; (IM+PO): 3.3% vs 11.9% Vomiting (IM only): 3.3% vs 0; (IM+PO): 10% vs 0% Somnolence (IM only): 0 vs 0; (IM+PO): 1.1% vs 0% Tachycardia (IM only): 2.2% vs 0 No patients had an increase in QTc interval ≥20% or had an interval >500ms during IM or PO treatment Mean change in QTc interval from baseline to end of IM treatment: +2.14 ms vs +2.22 ms Elevated glucose (>1.2 ULN): 12% vs 13% over both treatments
Costa, 2007 Brazil	NR	NR

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Brook, 2000 International	16 patients total (8.9% in ziaprasidone and 8.9% in haloperidol) ; 4 in ziprasidone and 1 in haloperidol (none during the IM period) Discontinuation reasons, ziprasidone PO: 1 pt (1.1%) discontinued due to severe postural hypotension; 1 pt (1.1%) discontinued due to akathisia; 1 pt (1.1%) with a history of dystonic reactions with neroleptic treatment discontinued due to laryngospasm in association with acute dystonia Discontinuation reasons, haloperidol PO: 1 pt (2.4%) discontinued due to excessive sweating and dry mouth	
Costa, 2007 Brazil	Total withdrawals 14% (9) Withdrawals due to AEs - NR	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Covington, 2000 U.S. (Poor)	haloperidol	clozapine, dose not reported haloperidol, dose not reported	NR/ NR	Premorbid Asocial Adjustment Scale SANS QLS Assessments at baseline, 6 weeks, 6 months, 12 months, and 24 months
Csernansky, 2002 U.S. Risperidone-USA-79 Study	haloperidol	risperidone 2-8 mg/day; mean modal dose 4.9 mg/day haloperidol 5-20 mg/day; mean modal dose 11.7 mg/day Duration 1 year	NR/ NR	Relapse rates and time to first relapse; PANSS, CGI
Currier, 2001 U.S.	haloperidol	risperidone 2mg + lorazepam 2mg PO haloperidol 5mg + lorazepam 2mg IM Duration: 24 hours	NR/ NR	PANSS CGI

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Covington, 2000 U.S. (Poor)	Mean change in score , clozapine vs haloperidol: SANS at 12 months: -0.83 vs -0.01 SANS at 24 months: -0.38 vs -0.08 QLS at 12 months: +0.29 vs +0.20 QLS at 24 months: +0.37 vs +0.18
Csernansky, 2002 U.S. Risperidone-USA-79 Study	Proportion of patients who relapsed, risperidone vs haloperidol: 25.4% vs 39.9%. Relapse risk ratio in haloperidol was 1.93 times than risk in risperidone (95% CI 1.33-2.80, p<0.001). Mean PANSS total and subscale scores at one year or last study rating improved in risperidone and worsened in haloperidol. The data was shown in bar graph only with p-values, but endpoint or change scores were not shown. The differences between treatments were statistically significant for PANSS total and 4 subscale scores.
Currier, 2001 U.S.	baseline vs 30-min vs 60-min, Mean(SD), 95%CI Combined Psychotic Agitation Score: haloperidol: 28.5(5.7), 26.4-30.6 vs 14.0(8.9), 10.3-16.9 vs 8.2(5.7), 6.0-10.3 risperidone: 26.7(5.2), 24.8-28.7 vs 15.9(9.6), 12.3-19.6 vs 10.1(8.2), 7.0-13.3 *p<0.0001 vs baseline; p=NS between groups PANSS-hallucinatory: haloperidol: 4.7 vs 2.7 vs 1.7; risperidone: 5.1 vs 2.9 vs 1.8 PANSS-hostility: haloperidal: 5.3 vs 2.2 vs 1.4; risperidone: 4.9 vs 2.8 vs 1.7 PANSS-uncooperativeness: haloperidal: 5.8 vs 3.2 vs 1.5; risperidone: 5.3 vs 2.7 vs 1.9 PANSS-excitement: haloperidol: 6.0 vs 2.9 vs 1.7; risperidone: 5.9 vs 3.6 vs 2.1 PANSS-impulsiveness: haloperidol: 6.3 vs 3.2 vs 1.8; risperidone: 6.1 vs 3.9 vs 2.2 *p<0.0001 vs baselind; p=0.42 between groups CGI: 15-min vs 30-min vs 60-min vs 120-min, Mean(SD), 95%CI haloperidol: 4.21(1.23), 3.74-4.68 vs 2.9(0.9), 2.56-3.24 vs 2.31(0.6), 2.08-2.54 vs 2.21(0.94), 1.85-2.56 risperidone: 4.17(1.23), 3.71-4.64 vs 3.28(1.10), 2.86-3.70 vs 2.52(1.09), 2.10-2.93 vs 2.10(0.41), 1.95-2.26 *p<0.0001 vs baseline; p=0.419 between groups

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Covington, 2000 U.S. (Poor)	Not reported	Not reported
Csernansky, 2002 U.S. Risperidone-USA-79 Study	Monitoring for AEs, a battery of standard laboratory tests, electrocardiography, and physical exam, ESRS.	Antiparkinsonian drugs prescribed for 30 consecutive days for 17.6% in haloperidol vs 9.0% in risperidone (p=0.02). Other AEs, risperidone vs haloperidol: Somnolence 14% vs 25% (p.nr) Agitation 10% vs 18% (p.nr) Mean change in weight: +2.3 kg vs -0.73 (p<0.001)
Currier, 2001 U.S.	Monitored by study staff and clinicians	risperidone vs haloperidol, Mean(SD) Somnolence: NS between groups Time to sleep (min): 43(25.1) vs 44.3(25.6) dystonia within 24 hours (no. of patients): 0 vs 1

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Covington, 2000 U.S. (Poor)	Not reported	
Csernansky, 2002 U.S. Risperidone-USA-79 Study	Risperidone vs haloperidol, Total withdrawals: 59.4 vs 77.3% (p<0.0001) Due to AEs: 15.4% vs 12.4% (ns)	
Currier, 2001 U.S.	NR	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Daniel, 2004 U.S.	haloperidol	ziprasidone IM 20-80 mg/day haloperidol IM 10-40 mg/day Duration: 7 days	NR/ NR	BPRS
Essock, 2000 Essock, 1996 Covell, 2004 Jackson, 2004 U.S. Inpatients	risperidone; conventional AP (all lumped together as "usual care")	clozapine Mean and median doses: clozapine: 486mg/d and 517mg/d Duration: 2 years	NR/ NR	Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression (CGI) Quality of Life Inventory Abnormal Involuntary Movement Scale (AIMS) Assessments made every 4 months

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Daniel, 2004 U.S.	BPRS: NR, NS
Essock, 2000 Essock, 1996 Covell, 2004 Jackson, 2004 U.S. Inpatients	Treatment Intolerence (TI); Treatment nonresponsive (TNR) treatment persistent over 2 years: TI-clozapine: 44% TI-usual care: 37% TNR-clozapine: 70% TNR-usual care: 30% *p<0.0001 1-year discharge rates: 27% for clozapine patients and 30% for control group (p=NS) after discharge, 3% of clozapine group re-admitted in first 6-months post-discharge 29% of control group re-admitted in first 6 months post-discharge p for clozapine vs control on re-admittance: p<0.001

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Daniel, 2004 U.S.	COSTART Simpson-Angus Scale Barnes Akathisia Scale	Z-20mg vs Z-40mg vs Z-80mg vs H-20-40mg, no(%) Adverse event at any time: 50(80%) vs 60(85%) vs 58(88%) vs 85(85%) Adverse event on IM treatment: 49(71%) vs 57(80%) vs 55(83%) vs 77(77%) Akathisia: 4(6%) vs 4(6%) vs 8(12%) vs 21(21%) Dystonia: 5(7%) vs 2(3%) vs 2(3%) vs 10(10%) EPS: 0(0%) vs 1(1%) vs 3(4%) vs 15(15%) Hypertonia: 1(1%) vs 1(1%) vs 2(3%) vs 11(11%) Anxiety: 11(16%) vs 10(14%) vs 11(17%) vs 13(13%) Dizziness: 11(16%) vs 14(20%) vs 10(15%) vs 0(0%) Headache: 12(17%) vs 10(14%) vs 13(20%) vs 8(8%) Injection-site pain: 4(6%) vs 7(10%) vs 11(17%) vs 2(2%) Insomnia: 7(10%) vs 11(15%) vs 14(21%) vs 12(12%) Nausea: 9(13%) vs 14(20%) vs 12(18%) vs 3(3%) Tachycardia: 2(3%) vs 8(11%) vs 5(8%) vs 6(6%) Vomiting: 6(9%) vs 8(11%) vs 8(12%) vs 5(5%)
Essock, 2000 Essock, 1996 Covell, 2004 Jackson, 2004 U.S. Inpatients	NR Weight information collected from charts	Clozapine vs usual care EPS-free months during 2 years: 18 months vs 14 months, p=0.001 Disruptiveness-free months during 2 years: 10 months vs 6 months, p<0.001 Change in total BPRS during 2 years: 1 vs 3, p=NS 18% of TI patients taking clozapine developed blood dyscrasia vs 3% of TNR pts 15% of TI patients taking clozapine developed either agranulocytosis or severe leukopenia vs 3% of clozapine TNR patients Crossover-excluded analysis Weight loss or no change in weight over 24 months: Clozapine men vs women: 25% vs 29% Usual care men vs women: 19% vs 24% Weight gain 0%<gain<20% of baseline weight over 24 months: Clozapine men vs women: 62% vs 42% Usual care men vs women: 79% vs 68% Weight gain ≥20% of baseline weight over 24 months: Clozapine men vs women*: 13% vs 29% Usual care men vs women: 2% vs 8% (*p<0.01)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Daniel, 2004 U.S.	Z-20mg vs Z-40mg vs Z-80mg vs H-20-40mg, no(%) Total withdrawals: 7(10%) vs 10(14%) vs 11(17%) vs 10(10%) Withdrawals due to AEs: 0 vs 1 vs 2 vs 1	Concomitant lorazepam (oral or IM up to 12 mg/day) fpr agitation and temazepam (up to 30 mg/night) for insomnia were allowed if needed. Benztropine and propranolol were allowed for the treatment of extrapyramidal symptoms and akathisia, respectively,
Essock, 2000 Essock, 1996 Covell, 2004 Jackson, 2004 U.S. Inpatients	Treatment discontinuation [Treatment Intolerence (TI); Treatment nonresponsive (TNR)]: TI-clozapine > TNR-clozapine, p<0.05 for discontinuation due to agranulocytosis or severe leukopenia TI-clozapine > TNR-clozapine, p<0.01 excluding individuals who stopped due to agranulocytosis or leukopenia	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Glick, 2002 (See Tollefson, 1997)		olanzapine 5-20 mg/day haloperidol 5-20 mg/day risperidone 4-12 mg/day Duration: 6 weeks		
Goff, 1998 U.S.	haloperidol	ziprasidone 4-160 mg/day haloperidol 15 mg Duration: 4 weeks	NR/ 4-7 days	Primary efficacy parameters: BPRS, CGI-S
Green, 2002 Marder, 2003 U.S.	haloperidol	risperidone 6-16 mg/day, mean dose 5.0 mg/day haloperidol 6-16 mg/day, mean dose 6.0 mg/day Duration 2 years	2-month run-in on haloperidol	BPRS, SANS, SCL-90-R (subjective self-report instrument) Assessments conducted at pretreatment, 9 months, 15 months, and 24 months Neurocognitive battery at baseline and weeks 4, 24, 48, 72, and 104: Perceptual discrimination Memory and verbal fluency Executive (Wisconsin Card Sorting Test)
Hamilton, 1998 (See Beasley, 1996)	See Beasley, 1996	See Beasley, 1996 Duration 24 weeks	See Beasley, 1996	BPRS, SANS, CGI severity at baseline and weekly visits QLS

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Glick, 2002 (See Tollefson, 1997)	
Goff, 1998 U.S.	Mean change from baseline score: Z-4mg vs Z-10mg vs Z-40mg vs Z-160mg vs H-15mg BPRS total: -5.7 vs -5.4 vs -5.7 vs -11.9 vs -11.6 BPRS core: -3.6 vs -2.8 vs -3.3 vs -5.8 vs -5.4 CGI severity: -0.1 vs -0.2 vs -0.2 vs -1.2* vs -1.1** *p=0.001 vs Z-4mg; **p<0.01 vs Z-4mg response rate-BPRS(%): 36.8 vs 29.4 vs 29.4 vs 45.0 vs 47.1 response rate-CGI (%): 15.8 vs 11.8 vs 11.8 vs 50.0 vs 41.2
Green, 2002 Marder, 2003 U.S.	Risperidone vs haloperidol, change in mean score: BPRS Total -0.14 vs -0.14 (ns) BPRS Anxious depression -0.29 vs +0.03 (p=0.02) SANS Global -0.19 vs -0.15 (ns) SCL-90-R Global symptom index -0.33 vs -0.02 (p<0.01) SCL-90-R Phobic anxiety -0.21 vs 0.12 (p=0.01) SCL-90-R Anxiety -0.28 vs 0.07 (p<0.01) SCL-90-R Depression -0.49 vs -0.03 (p<0.01) Relapse-free after 2 years: 88% in risperidone and 73% in haloperidol (ns) Neurocognitive effects: no differences between groups. (Positive change = improvement) Perceptual discrimination at Week 140: -.002 vs -0.126 (ns) Memory and fluency at week 104: 0.311 vs 0.381(ns) Executive functioning at week 104: 0.098 vs 0.187 (ns)
Hamilton, 1998 (See Beasley, 1996)	Mean change in score at 24 week extension (baseline to LOCF) olanzapine (low, medium, high) vs haloperidol: BPRS total score (-15.0, -22.8, -19.9) vs -19.9 (ns) SANS summary score (-2.5, -4.7, -5.5) vs -2.7 (p = 0.049 for Olz-H) CGI severity score (-1.1, -1.6, -1.2) vs -0.9 (ns) QLS total score (+6.7, +24.6, +15.5) vs +4.9 (ns) QLS intrapsychic foundations (+2.3, +8.1, +4.2) vs +0.9 (ns) QLS interpersonal relations (+2.5, +9.3, +5.9) vs +3.1 (ns) QLS instrumental role category (+1.5, +5.6, +4.0) vs +0.9 (ns) QLS common objects and activities (+0.4, +1.7, +1.4) vs 0.0 (ns)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Glick, 2002 (See Tollefson, 1997)		
Goff, 1998 U.S.	Abnormal movements: Simpson-Angus Scale Barnes Akathisia Scale Involuntary Movement Scale (AIMS)	z-4mg vs z-10mg vs z-40mg vs z-160mg vs h-15mg 66(73.3%) experienced an adverse event during the study, and 36 were considered to be related to study treatment: 9 vs 3 vs 7 vs 8 vs 9 Simpson-Angus Scale, mean change: -1.8 vs -1.2 vs 1 vs -0.5 vs 1 Barnes Akathisia Scale, mean change: -0.7 vs -0.1 vs 1 vs 4 vs 2 AIMS, mean change: -0.1 vs 0.7 vs 0.3 vs -0.5 vs -0.9
Green, 2002 Marder, 2003 U.S.	AIMS, BAS, Modified SARS Social functioning: Social Adjustment Scale and QLS. Assessments conducted at pretreatment, 9 months, 15 months, and 24 months	risperidone vs haloperidol, SARS scale: Tremor -0.28 vs -0.04 (p=0.01) Akathisia -0.39 vs 0.04 (p<0.01) BAS Global -0.55 vs 0.10 (p<0.01)
Hamilton, 1998 (See Beasley, 1996)	See Beasley, 1996	Not reported

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Glick, 2002 (See Tollefson, 1997)		
Goff, 1998 U.S.	Total withdrawals: 46(51%) total Withdrawals due to AEs: Z-4mg(1), Z-160mg(1), haloperidol(1)	
Green, 2002 Marder, 2003 U.S.	32 total; due to AEs not reported	
Hamilton, 1998 (See Beasley, 1996)	Due to AEs: 2 in olanzapine (low) 3 in olanzapine (medium) 2 in olanzapine (high) 4 in haloperidol 3 in placebo	Results represent patients who responded during acute phase and continued in extension phase.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Hertling, 2003 Germany & Austria	flupenthixol	risperidone 2-6 mg/day (mean dose 3.6 mg/day). flupenthixol 4-12 mg/day (mean dose 6.6 mg/day). Duration 25 weeks	NR/ NR	Quality of life: EuroQuol-Visual Analogue Scale at weeks 0, 4, 8, 12, 16, 20, and 24 Attitude towards trial medication: DAI-30 at Weeks 0, 2, 4, 12, and 24 Patient satisfaction: at week 24
Hirsch, 2002 U.K.	haloperidol	ziprasidone 80-160 mg/day; modal dose 80 mg/day; mean dose at week 28 = 116.5 mg/day haloperidol 5-15 mg/day; modal dose 5 mg/day; mean dose at week 28 = 8.6 mg/day Duration 28 weeks	3- to 14-day run-in between screening and baseline.	PANSS at screening, baseline, weeks 3,6,16, and 28 MADRS and CGI at baseline and weeks 3,6,16, and 28 QLS at baseline and week 28 LOCF analysis
Kane, 2006 India	chlorpromazine	6 weeks of prospective open-label treatment with haloperidol <=30 mg/day. Followed by up to 12 weeks of double-blind treatment with either ziprasidone, up to 160 mg/day, or chlorpromazine, up to 1200 mg/day.	NR	Brief Psychiatric Rating Scale (BPRSd) total score derived from the Positive and Negative Syndrome Scale (PANSS), BPRSd core psychotic symptoms, and Clinical Global Impression-Severity (CGI-S). Secondary efficacy variables included PANSS total score, PANSS Negative Subscale, and the MADRS performed at screening, baseline, weeks 3 and 6 of the haloperidol treatment phase, and weeks 3, 6, 9 and 12 (or at early termination) of the double-blind treatment phase.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Hertling, 2003 Germany & Austria	EuroQuol index increased in both groups; no significant differences between groups. Increase in DAI-30 mean score 1.4 points (6.9%) in risperidone vs 2.5 points (20%) in flupenthixol. More in flupenthixol had improved ability to cope with stress (p<0.05); felt more relaxed (p<0.05) and the ability to achieve something (p<0.05). No sig. differences between Rx groups in patient satisfaction. See comments regarding efficacy and side effects.
Hirsch, 2002 U.K.	ziprasidone vs haloperidol, Mean change in score: PANSS total -9.1 vs -8.1 (ns); negative subscale -3.6 vs -3.0 (ns) BPRSd core items -1.5 vs -1.3 (ns); CGI-Severity 0.5 vs 0.4 (ns) MADRS -1.6 vs -0.6 (ns); GAF +3.2 vs +2.5 (ns); QLS +2.8 vs +0.9 (ns) Negative symptom responders (>=20% decrease in PANSS negative subscale) 48% vs 33% (p<0.05)
Kane, 2006 India	6 weeks CGI-S Ziprasidone vs chlorpromazine P < 0.05 12 weeks PANSS negative Ziprasidone vs chlorpromazine P < 0.05 12 weeks change in MADRS Ziprasidone vs chlorpromazine -0.63 and -1.07 P = NS, BPRSd response rate at 12 weeks Ziprasidone vs chlorpromazine ≥ 20% 57.85 vs55.37 ≥ 30% 47.10 vs. 45.45 ≥ 40% 39.67 vs. 32.23 ≥ 50% 27.7 vs. 21.48

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Hertling, 2003 Germany & Austria	See comments	See comments
Hirsch, 2002 U.K.	COSTART BAS, SARS at baseline and weeks 6, 16, and 28. AIMS at baseline, wk 28. Lab tests wks 4, 12 ECG at weeks 12 & 28; QTc calculated	ziprasidone vs haloperidol, Movement disorders: 15% vs 41% (p<0.001) Insomnia 16% vs 18% (ns) Somnolence 14% vs 9% (ns) Vomiting 11% vs 6% (ns) Nausea 10% vs 4% (p=0.042) Weight change +0.31 kg vs +0.22kg (ns)
Kane, 2006 India	All patient reported AEs were rrecorded. Laboratory tests at screening, week 6 of the open-phase and week 12 of the double-blind phase, Clinically significant changes in physical examination findings were considered adverse events. Electrocardiograms were performed at screening of open phase and at baseline, and at weeks 1, 3, 6 and 12, or early termination of the double-blind phase. Vital signs were monitored.	Ziprasidone vs. chlorpromazine n(%) Akathisia 9(5.9) vs. 13(8.4) Amenorrhea 1(2.0) vs. 4(12.1) Dizziness 9(5.9) vs. 19(12.3) EPS 49(32.2) vs. 54(35.1) Male sexual dysfunction 7(6.9) vs.3(2.5) Postural hypotension 3(2.0) vs. 8(5.2) Somnolence 29(19.1) vs. 44(28.6) Tardive dyskinesia 13(8.6) vs. 16(10.4) Tremor 14 (9.2) vs. 6(3.9) Weight gain 3(2.0) vs. 10(6.5) Vomiting 8(5.3) vs. 6 (3.9)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Hertling, 2003 Germany & Austria	See comments	Study subjects were patients with negative symptoms. A previous publication of this trial (Philipp 2002) reported the methods and results of efficacy and side effects, but was excluded from review because of non-English language.
Hirsch, 2002 U.K.	171 total, 36 Due to AEs: 12 in ziprasidone (1 with movement disorders) 24 in haloperidol (7 with movement disorders)	
Kane, 2006 India	Open label phase Over all withdrawals = 108 Withdrawals due to AEs = 5 Double-blind phase Over all withdrawals = 35 Withdrawals due to AEs Ziprasidone = 6 Chlorpromazine = 8	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Kane, 2002 U.S.	haloperidol	Aripiprazole 15 mg/d Aripiprazole 30 mg/d Haloperidol 10 mg/d Duration: 4 weeks	NR/5-7 days	Primary variables: PANSS total, positive and CGI-S scores timing of assessment: day 7, 14, 21, 28 Other variables: PANSS negative , PANSS-derived Brief Psychiatric Rating Scale (BPRS), mean CGI scores and responder rates (patients with a CGI-I score of 1 or 2 or a >= 30% decrease from baseline in PANSS total score were considered responders)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Kane, 2002 U.S.	PANSS total, p vs placebo (Placebo: -2.9) aripiprazole 15mg: -15.5, p<0.001 aripiprazole 30mg: -11.4, p=0.009 haloperidol 10mg: -23.8, p=0.001 PANSS positive, p vs placebo (Placebo: -0.6) aripiprazole 15mg: -4.2, p<0.001 aripiprazole 30mg: -3.8, p=0.001 haloperidol 10mg: -4.4, p<0.001 PANSS negative, p vs placebo (Placebo: -1.2) aripiprazole 15mg: -3.6, p=0.006 aripiprazole 30mg: -2.3, p=0.213 haloperidol 10mg: -2.9, p=0.043 PANSS-derived BPRS score, p vs placebo (Placebo: -1.1) aripiprazole 15mg: -3.1, p=0.001 aripiprazole 30mg: -3.0, p=0.001 haloperidol 10mg: -3.5, p<0.001 CGI-Severity, p vs placebo (Placebo: -0.1) aripiprazole 15mg: -0.6, p<0.001 aripiprazole 30mg: -0.4, p=0.019 haloperidol 10mg: -0.5, p=0.002 CGI-Improvement, p vs placebo (Placebo: 4.3) aripiprazole 15mg: 3.5, p<0.001 aripiprazole 30mg: 3.8, p=0.016 haloperidol 10mg: 3.7, p=0.002 Responder rate (%), p vs placebo (Placebo: 17) aripiprazole 15mg: 35, p=0.002 aripiprazole 30mg: 28, p=0.050 haloperidol 10mg: 26, p=0.089

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Kane, 2002 U.S.	EPS: Simpson-angus Scale, Barnes Akathisia Scale, adnd the Abnormal Involuntary Movement Scale Timing of assessment\: baseline and weekly	aripiprazole 15mg vs aripiprazole 30mg vs haloperidol 10mg vs placebe headache: 24(24%) vs 29(29%) vs 26(25%) vs24(23%) anxiety: 23(23%) vs 17(17%) vs 20(19%) vs 16(15%) insomnia: 19(19%) vs 22(22%) vs 25(24%) vs 18(17%) nausea: 15(15%) vs 14(14%) vs 6(6%) vs 7(7%) dizziness: 13(13%) vs 17(17%) vs 6(6%) vs 6(6%) abdominal pain: 9(9%) vs 6(6%) vs 6(6%) vs 5(5%) vomiting: 8(8%) vs 17(17%) vs 10(10%) vs 10(10%) akathisia: 8(8%) vs 12(12%) vs 24(23%) vs 11(11%) somnolence: 5(5%) vs10(10%) vs 13(13%) vs4(4%) asthenia: 3(3%) vs 6(6%) vs 5(5%) vs 3(3%) orthostatic hypotension: 2(2%) vs 7(7%) vs 1(1%) vs 3(3%) hypertonia: 2(2%) vs 8(8%) vs 3(3%) vs 5(5%) tremor: 2(2%) vs 3(3%) vs 7(7%) vs 3(3%) blurred vision: 1(1%) vs 2(2%) vs 8(8%) vs 1(1%) EPS related AEs: 18(18%) vs 20(20%) vs 37(36%) vs 22(21%) benztropine required for EPS: 8% vs 15% vs 30% vs 12% Body weight: Mean change form baseline (kg): 0.4 vs 0.9 vs 0.5 vs 0.2 >7% increase from baseline, % patients: 7* vs 4 vs 10** vs 1 (*p<0.05; **p<0.01 vs placebo) Prolactin level: Mean change from baseline (ng/dL): -7.0 vs -7.1 vs 22.5* vs -1.8 (*p<0.001 vs placebo) QTc interval: mean change form baseline (ms): -2.02 vs -3.38 vs 1.67 vs -3.45, NS QTc >= 450ms and a >= 10% increase (%): 0 vs 0 vs 3 vs 1 vital sign: NS

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Kane, 2002 U.S.	Withdrawals due to AEs for total N: 11% (45/414 pts); Withdrawls due to AEs: Aripiprazole 15mg: 9% (9 pts); Aripiprazole 30mg: 8% (8 pts); Haloperidol: 11% (11 pts); Placebo: 16% (17 pts)	Use of psychotropic agents was prohibited throughout the washout and treatment periods of the study, except for lorazepam for anxiety or insomnia. Lorazepam, administered intramuscularly, was also permmited for emerging agitation. Benztropine treatment was allowed for EPS, if judged necessary by the investigator. The dose was limited to a maximum of 6 mg per daym and was only permitted during the treatment phase of the study

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Kane, 2007 RCT, DB Multicenter (59 centers in US & Canada)	perphenazine	aripiprazole: 15-30 mg/d started at 15 mg/d and dose adjustments could be made to 30 mg/d at end of week 1 perphenazine: 8-64 mg/d started at 8 mg/d and could be increased to 16 mg/d on day 4 if needed; at end of week 1, dose (in 8 mg/d) increments) could be made at 4- to 7-day intervals up to 64 mg/d Duration: 6 weeks (baseline = end of placebo washout period)	Single blind placebo washout period lasting 2-10 days	PANSS total, PANSS-derived BPRS, CGI-S, CGI-I, QLS

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Kane, 2007	aripiprazole vs. perphenazine, mean and 95% CI
RCT, DB Multicenter (59 centers in US & Canada)	PANSS total score Baseline: 97.5 (95.0 to 100.0) vs. 99.5 (97.0 to 102.1) Change at week 6: -9.8 (-13.2 to -6.3) vs. -10.5 (-14.0 to -7.0) PANSS-derived BPRS core score Baseline: 17.2 (16.7 to 17.7) vs. 17.6 (17.0 to 18.1) Change at week 6: -2.0 (-2.7 to -1.3) vs. -2.0 (-2.7 to -1.3) CGI-S score Baseline: 5.0 (4.9 to 5.2) vs. 5.0 (4.8 to 5.1) Change at week 6: -0.3 (-0.5 to -0.2) vs. -0.3 (-0.5 to -0.1) CGI-I score Score at week 6: 3.7 (3.4 to 3.9) vs. 3.5 (3.3 to 3.7) 27% (n=40) of aripiprazole-treated patients and 25% (n=36) of perphenazine-treated patients were classified as treatment responders according to CGI or PANSS measures after 6 wks Mean change in QLS score from baseline (aripiprazole vs. perphenazine): 1.7 vs. 2.6 Proportion of patients experiencing clinically important improvement in QLS (>/= 20% increase in QLS score from baseline): 36% in aripiprazole vs. 21% in perphenazine group; P=0.052.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Kane, 2007 RCT, DB Multicenter (59 centers in US & Canada)	Review of AE reports (including intercurrent illness), vital sign measurement, ECG, body weight, concomitant medication use, and results of physical exams and lab tests. EPS assessed using SAS, AIMS, and BAS.	Treatment -emergent adverse events aripipazole (n=153) vs. perphenazine (n=144) Insomnia: 24.2% vs. 20.8% Agitation: 16.3% vs. 16.7% Headache: 16.3% vs. 9.0% Psychosis: 11.8% vs. 9.7% Anxiety: 10.5% vs. 12.5% Dyspepsia: 10.5% vs. 6.3% Creatine phosphokinase increased: 5.9% vs. 2.8% Akathisia: 3.9% vs. 9.0% Extrapyramidal syndrome: 3.3% vs. 6.3% Somnolence: 2.6% vs. 6.9% Lightheadedness: 1.3% vs. 6.9% Accidental injury: 1.3% vs. 6.3% Received concomitant meds for EPS: 17.6% vs. 27.8% SAS scores showed mean improvement from baseline in aripiprazole group but worsened in perphenazine group. Mean change from baseline to endpoint difrered significantly between aripiprazole and perphenazine groups (P=0.04). Changes in AIMS and BAS scores not significantly different between treatment groups. Body weight: no significant differences between treatments in terms of weight change; both groups showed a mean decrease in body weight.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Kane, 2007 RCT, DB Multicenter (59 centers in US & Canada)	Total withdrawals: 75 (25%) aripiprazole: 44 (28.6%) perphenazine: 31 (21.2%) Withdrawals due to AEs: 33 (11%) aripiprazole: 22 (14.3%) perphenazine: 11 (7.53%)	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Kasper, 2003 Malhorta, 2005 poster (remission rates) International	haloperidol	aripiprazole 30 mg/d; mean dose 29.01 mg/d haloperidol 5 mg/d days 1-3; 10 mg/d day 4 onward; mean dose overall 8.90 mg/day Duration 52 weeks	NR; 5-day placebo washout for oral agents; washout for depot: one depot cycle plus one week	Primary outcome: time to failure to maintain response in responders. Response criteria required a >=20% decrease from baseline PANSS total at any single timepoint, provided that patients did not concurrently have 1) a CGI score of 6 or 7, or 2) an AE of worsening schizophrenia, or 3) a score of 5, 6, or 7 in at least one of the 4 PANSS psychotic subscale. Criteria for failure was a positive result on any of items 1, 2, or 3 above. Additional response criteria as the former, except >=30% decrease in PANSS was required.
Kinon, 2004 U.S. Inpatients	haloperidol + lorazepam	olanzapine 10-20 mg po qd + lorazepam (Mean dose for olanzapine: 17.1mg and mean dose lorazepam: 2.6 mg) haloperidol 10-20 mg po qd + lorazepam (Mean dose for haloperidol: 15.7mg and mean dose lorazepam: 2.94 mg) lorazepam decreased until no patient received it during days 18-21 3 week duration	24hr washout	Primary efficacy: PANSS Agitation at 1,4, 8, 16, and 24hrs, daily for first week, and once/week for weeks 2 and 3. Secondary outcomes: CGI-Severity and Improvement Scales, Overt Agitation Severity Scale (OASS), and Nurses Obsercation Scael for Inpatient Evaluation (NOSIE). Other measurements: frequency of time in restraints or seclusion and special nursing watch, and frequency of lorazepam treatment. DAI-10 (Drug Attitude Inventory) used for patient response to medication.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Kasper, 2003 Malhorta, 2005 poster (remission rates) International	Response criteria, aripiprazole vs haloperidol >20% improvemtn in PANSS at a single timepoint: 72% vs 69%, NS >30% improvement in PANsS maintained for > 28 days plus one additional visit: 52% vs 44%, p=0.003 Time to failure to maintain response; risk ratio >20% improvement in PANSS: 77% vs 73%; 0.88; NS > 30% improvement in PANSS: 85% vs 79%; 0.70; NS Mean change from baseline to week 52 PANSS negative score: -5.3 vs -4.4, p<0.05 MADRS total score: -2.7 vs -1.4, p<0.05 Remission rate (% pts): 32% vs 22%; p<0.001 (Malhotra 2005 poster)
Kinon, 2004 U.S. Inpatients	olanzapine vs haloperidol Mean change in score (SD): PANSS Agitiation scores, at 1 hour: -5.79 vs -4.89 (p<0.001) At day 21 (LOCF): -14.00(10.71) vs -11.21(11.67), p=0.044 PANSS Total score: -20.73(10.81) vs -16.03(13.76), p=0.51 OASS: improvement olan > hal for items: fidgeting and perseverating (p=0.41 and p=0.50 respectively) Days (SD) to discharge: 13.73 (2.43) days vs 13.13 (3.75) days, p=NS Proportion of patients using restraints, seclusions, or special nursing watch: 17.3% vs 16.7%, p=NS Mean number of hours (SD) used per patient per day: 1st week: 1.57 (5.52) vs 2.59 (6.79) 2nd week: 0.33 (2.23) vs 0.92 (4.05) 3rd week: 0 vs 0.55 (2.74) Mean baseline to end-point changes in NOSIE: -8.88 (15.82) vs -7.74 (16.82), p=NS Patient scores for satisfaction with medication at end-point: +0.61 vs-0.72, p=0.52

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Kasper, 2003 Malhorta, 2005 poster (remission rates) International	Standard clinical assessments, vital signs, and movement assessments evaluated. SAS, AIMS, BAS at each study visit. ECG recordings and routine lab tests (hematology, serum chemistry, and urinalysis) at screening and weeks 2, 8, 18 (not ECG), 26, 38, and 52. Physical exams at weeks 8, 26, and 52. Plasma prolactin levels at baseline, weeks 2, 8, 18, 26, 38, and 52.	Adverse event, aripiprazole vs haloperiodol Weight gain: 44(5%) vs 14(3%), NS Insomnia: 185(22%) vs 88(20%), NS Psychosis: 156(18%) vs 70(16%), NS Akathisia: 111(13%) vs 108(25%), p<0.001 Anxiety: 108(13%) vs 50(12%), NS EPS: 84(10%) vs 130 (30%), p<0.001 Mean change at week 52 (LOCF): SAS: -0.2 vs 1.9, p<0.001 AIMS: -0.3 vs 0.2, p<0.001 BAS: 0.0 vs 0.4, p<0.001
Kinon, 2004 U.S. Inpatients	Treatment-emergent AEs, changes in vital signs, and laboratory analyses recorded. EPS measured by the Simpson-Angus Scale and the Barnes Akathisia Scale. Change in alterness or sedation assessed with the Tranquilization Scale (modified)	olanzapine vs haloperidol Patients reporting all treatment-emergent AEs: 67.3% vs 85.4%, p=0.38 Weight gain: +2.8kg vs -0.64kg, p<0.001 Simpson-Angus: -0.41(2.18) vs +0.64(3.53), p=NS Patients receiving antiparkinsonian mediations: 0% vs 8.3%, p=0.05 Mean change in Barnes-Akathisia scale : olanzapine only reported: -1.34 Dystonia: 0% vs 8.3%, p=0.05 Hypertonia: 0% vs 8.3%, p=0.05 Increased salivation: 0% vs 8.3%, p=0.05 Headache: 11.5% vs 25.0%, p=NS Nervousness: 7.7% vs 16.7%, p=NS Anxiety: 11.5% vs 4.2%, p=NS Insomnia: 5.7% vs 13.0%, p=NS Somnolence: 17.3% vs 25.0%, p=NS Pain: 9.6% vs 10.0%, p=NS Agitation: 9.6% vs 10.0%, p=NS

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Kasper, 2003 Malhorta, 2005 poster (remission rates) International	Aripiprazole vs haloperidol, Total withdrawals: 494 (57.4%) vs 305 (70.4%), p=0.0001 Due to AEs: 70 (8%) vs 80 (19%), p=0.001	
Kinon, 2004 U.S. Inpatients	Olanzapine vs haloperidol Total % of patients who discontinued (of original 100 patients, 43 dropped out): 32.7% vs 54.2% Withdrawals due to AEs: 1.9% vs 16.7%, p=0.013 Mean time to discontinuation: 17.69 days vs 14.21 days, p=0.016	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Lee, 1999 U.S.	Typical neuroleptics	clozapine mean dose 291.4 mg/day Typical APs, mean dose in chlorpromazine equivalents 488.3 mg/day Duration 12 months	NR/ NR	Schedule for Affective Disorders and Schizophrenia Lifetime (SADS-L) and Change (SADS-C) Cognitive test battery: Wechsler Adult Intelligence Scale Revised (WAIS-R), Consonant Trigram Test (CTT), Controlled Word Association Test (CWAT), Category Instance Generation Test (CIGT), Verbal List Learning (VLL) Immediate and Delayed Recall (VLL-IR, VLL-DR), Wisconsin Card Sorting Test (WCST), Wechsler Intelligence Scale for Children - Revised (WISC-R) at baseline, 6 weeks, 6 months, 12 months
Liberman, 2002 U.S.	haloperidol	Mean dosage: risperidone 8 mg haloperidol 20 mg Duration: 4 weeks	3 weeks/ NR	Activities of daily living (ADLs)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Lee, 1999 U.S.	Mean change in score, baseline to 12 months, clozapine vs typical APs (within-group p-values): BPRS -5.8 vs -5.5 Digital Symbol Substitution Test +1.9 (p<0.0001) vs +0.2 (ns) Consonant Trigram -1.0 vs +1.9 Category Instance Generation +6.0 (p<0.001) vs +3.2 (ns) Controlled Word Association Test +7.1 (p<0.0001) vs -0.6 (ns) VLL-IR +0.5 vs +0.6 VLL-DR +0.5 vs +1.3 WCST-Category +0.2 vs +0.9 WCST-Perseverative Error +5.5 vs +4.2 WISC-R Maze +1.0 vs +0.6
Liberman, 2002 U.S.	ADLs, dressing, grooming, room clean-up, showering: risperidone vs haloperidol: NR, NS both treatment improved vs baseline: showering, p=0.034; grooming, p=0.01 Neurocognitive performance: risperidone vs haloperidol: NR, NS

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Lee, 1999 U.S.	SARS, AIMS	Change in EPS score, baseline to 12 months, clozapine vs typical APs: EPS +0.3 vs +1.0 (no significant intra-group change in either treatment)
Liberman, 2002 U.S.	NR	NR

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Lee, 1999 U.S.	11 total; Due to AEs: none reported	
Liberman, 2002 U.S.	NR	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Lieberman, 2003a Green, 2004 Multi-site, North America and Western Europe	chlorpromazine	olanzapine 5-20 mg/day; mean modal dose 9.1 mg/day haloperidol 2-20 mg/day; mean modal dose 4.4 mg/day Duration 104 weeks	2-14 day washout	PANSS, MADRS, CGI severity assessed during washout and weekly through week 6, biweekly during weeks 7 through 12

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Lieberman, 2003a Green, 2004 Multi-site, North America and Western Europe	Results given are for the first 12-weeks only Mean change in score, olanzapine vs haloperidol: PANSS total: -20.0 vs -14.22 (ns) Negative scale: -2.95 vs -1.21 (ns) Positive scale: -7.41 vs -7.06 (ns) General scale: -9.85 vs -6.24 (ns) CGI severity: -1.34 vs -1.02 (ns) MADRS: -2.58 vs -1.83 (ns) Note: P-values are based on a last-observation-carried-forward analysis. A separate mixed-model analysis found statistical significance in the between-treatment differences for PANSS total, PANSS negative, PANSS general, and MADRS scores. Responder status by substance use disorder (SUD), alcohol use disorder (AUD), and Cannabis use disorder (CUD) Responder vs non-responder; RR (95% CI) Overall (treatments combined): patients with SUD: 27% vs 69%; non-SUD patients: 35% vs 65%; 1.12 (0.94-1.32) patients with AUD: 19% vs 81%*; non-AUD patients: 35% vs 64%; 1.26 (1.07-1.49) (*p<0.05) patients with CUD: 28% vs 72%; non-CUD patients: 34% vs 66%; 1.08 (0.90-1.29) haloperidol patients: SUD: 31% vs 69%; non-SUD: 32% vs 68%; 1.01 (0.80-1.29) AUD: 27% vs 73%; non-AUD: 33% vs 67%; 1.10 (0.85-1.42) CUD: 32% vs 68%; non-CUD: 31% vs 69%; 0.99 (0.76-1.28) olanzapine patients: SUD: 23% vs 77%; non-SUD: 38% vs 62%; 1.24 (0.98-1.57) AUD: 9% vs 91%*; non-AUD: 38% vs 62%; 1.47 (0.21-1.79) (*p<0.05) CUD: 24% vs 76%; non-CUD: 36% vs 64%; 1.18 (0.92-1.50)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Lieberman, 2003a Green, 2004 Multi-site, North America and Western Europe	COSTART, SAS, AIMS, BAS at each assessment	Results given for the first 12 weeks only Change in score, olanzapine vs haloperidol: SARS 0.00 vs +1.44 (p=0.001) BAS -0.13 vs 0.50 (p<0.001) Weight (kg) +7.30 vs +2.64 (p<0.001) Incidence of parkinsonism 26.1% vs 54.8% (p<0.001) Incidence of akathisia 11.9% vs 51.2% (p<0.001)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Lieberman, 2003a Green, 2004 Multi-site, North America and Western Europe	103 total; Due to AEs: 4 in olanzapine vs 9 in haloperidol Study completion rates for substance use disorder (SUD) vs non-SUD patients Haloperidol patients: SUD patients: 51% completed study vs 71% non-SUD patients (p<0.04) Olanzapine patients: SUD patients: 77% completed study vs 71% of non-SUD patients (p<0.53)	Younger population (mean age 23.8) with onset within past 5 years.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Lieberman, 2003b China	chlorpromazine	Median doses: clozapine 300 mg/day chlorpromazine 400 mg/day Duration: 52 weeks	28 days/ NR	Primary outcomes: remission measured bby BPRS and CGI Chinese version of: BPRS, Scake for Assessment of Negative Symptoms (SANS), CGI, Clobal Assessment of Function Scale (GAF), the Simpson Angus Extrapytamidal Symptoms Scale (SAESS)
Mahmoud, 2004 ROSE Group U.S.	Conventional AP	risperidone, mean dose NR Any one of 13 typical APs, selected by treating physician; all dosage forms including depot were permitted. Mean dose NR Duration 1 year After randomization, all mental health care, including all drug therapy, was provided according to the natural course of events in the community with only minimal protocol restrictions. Crossovers and combination therapy (2 or more AP medications in one day) were permitted.	NR/ NR	PANSS Patient satisfaction: Drug Attitude Inventory (DAI) Health-related quality of life (HRQOL) as measured by the SF-36, and the brief version of the QOL interview. Resource utilisation: acute psychiatric hospital days, non-hospital acute-care service days, routine mental health care, and medications. Data was recorded at schedule visits at baseline and at 4, 8, and 12 months following randomization.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Lieberman, 2003b China	clozapine vs chlorpromazine Remission: 65(81%) vs 63(79%) clozapine vs chlorpromazine, 95%CI Week 52 BPRS Total: 22.3 vs 22.1, (-2.5, 1.8) Anxiety/depression: 5.0 vs 5.0, (-0.5, 0.5) Anergy: 4.6 vs 4.9, (-0.5, 0.7) Thought disorder: 5.2 vs 5.1, (-1.0, 0.7) Agitation/Activation: 3.3 vs 3.4, (-0.2, 0.4) Hostility-paranoid: 4.2 vs 3.8 (-1.1, 0.3) SANS Total: 7.5 vs 9.5, (-1.9, 4.7) Affective flattening: 1.0 vs 2.2 (-0.0, 2.0) Poverty of thought: 0.4 vs 0.7 (-0.3, 0.7) Avolition: 3.0 vs 3.5 (-0.6, 1.5) Attention deficit: 0.3 vs 0.4 (-0.3, 0.5) Low level of interests: 2.8 vs 2.7 (-1.3, 1.0) CGI: 2.2 vs 2.0 (-0.6, 0.2) GAF: 72.4 vs 71.4 (-5.7, 4.8)
Mahmoud, 2004 ROSE Group U.S.	Change from mean baseline, risperidone vs typical Aps Total PANSS: -21.52 vs -14.43, p=0.0008 Postive symptom scale: -7.33 vs -5.15, p=0.0011 Negative symptom scale: -4.96 vs -3.05, p=0.0139 General psychopathology: -9.31 vs -6.21, p=0.0095 BAS: -0.34 vs -0.06, p=0.0275 SF-36 summary score: 7.09 vs 4.67, p=0.0326 Percentage of patients showing a 60% reduction in total PANSS score: Month 4: 11.0% vs 8.5%, NS Month 8: 16.3% vs 9.0%, p=0.007 Month 12: 20.9% vs 10.7%, p=0.001 Utilization parameters Mean number of days of combination therapy (2 or more AP medications in one day): 55.2 vs 57.0, NR % of patients who received no therapy during any portion of the follow-up: 94.8% vs 92.9%, NR Number of days without therapy, not necessarily consecutive: 110.2 vs 125, NR % of patients who used one or emore days of crossover therapy: 72.4% vs 41.4%, NR % of patients who remained in the study for >350 days: 84.5% vs 78.2%, p=0.02

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Lieberman, 2003b China	The Coding symbol and Thesaurus for Adverse Event Terminology (COSTART)	clozapine vs chlorpromazine (95%CI) EPS at Week 52 SAESS total: 0.28 vs 0.44 (-0.18, 0.44) Parkinsonian: 0.18 vs 0.33 (-0.11, 0.32) Other side effects at Week 52: SAESS dystonia: 0.07 vs 0.11 (0.10, 0.57) Blurred vision: 0.33 vs 0.46 (0.38, 0.74) Tense muscles: 0.06 vs0.08 (0.12, 0.87) Depressed affect: 0.25 vs 0.19 (1.00, 2.05) Sweating: 0.11 vs 0.06 (1.51, 6.10) Dry mouth: 0.32 vs 0.64 (0.17, 0.30) Akathisia: 0.09 vs 0.13 (0.26, 0.83) Objectively observed restlessness: 0.06 vs 0.09 (0.19, 0.85) Decreased urine production: 0.07 vs 0.12 (0.11, 0.47) Weight gain (kg): 9.9 vs 6.5, p=0.30
Mahmoud, 2004 ROSE Group U.S.	BAS, AIMS, SARS	No significant changes in tardive dyskinesia as measured by AIMS or differences in EPS as measured by SARS were observed in either group. The severity of drug-induced akathisia declined in both treatment groups, as measured by BAS.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Lieberman, 2003b China	Clozapine vs Chlorpromazine Total withdrawals: 10 vs 9 Withdrawals due to AEs: 2 vs 6	
Mahmoud, 2004 ROSE Group U.S.	Not reported	Effectiveness trial

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Mak, 2000 China	Conventional AP	risperidone conventional AP Duration: 3 months	1-2 weeks/ NR	BPRS Scale for Assessment of Positive Symptoms
Peuskens, 1999 Multi-national, Europe	Amisulpride	misulpride 800 mg/day risperidone 8 mg/day Duration 8 weeks	3-6 day single-blind placebo washout	PANSS, BPRS, CGI, Social & Occupational Functioning Assessment Scale (SOFAS), assessment of patients' subjective responses to treatment Change in BPRS >6 points = clinically relevant

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Mak, 2000 China	Baseline vs endpoint, p vs baseline BPRS: risperidone: 14.86(6.32) vs 9.59(4.42), p<0.0001 conventional AP: 14.16(6.34) vs 13.26(5.33), p>0.1 *risperidone vs conventional AP, p>0.1 Scale for Assessment of Positive: risperidone: 5.30(10.75) vs 1.14(2.62), p>0.05 conventional AP: 5(9.91) vs 4(8.02), p>0.5 *risperidone vs conventional AP, p>0.05 Scale for Assessment of Negative: risperidone: 53.82(11.62) vs 39.82(16.62), p<0.001 conventional AP: 51.50(12.73) vs 53.14(8.98), p>0.05 *risperidone vs conventional AP, p>0.05 Clinical Global Interview: risperidone: 3.95(0.64) vs 1.13(1.01), p<0.0001 conventional AP: 3.79(0.37) vs 3.63(0.57), p>0.1 *risperidone vs conventional AP, p<0.05
Peuskens, 1999 Multi-national, Europe	Mean change in score, risperidone vs amisulpride: BPRS total -15.2 vs -17.7 (p<0.0005) NS between groups on BPRS subscales PANSS positive -8.6 vs -9.6 (ns) PANSS negative -5.32 vs -6.9 (ns) 20% reduction in BPRS total achieved by 75% vs 78% (ns) 40% reduction in BPRS total achieved by 58% vs 67% (ns)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Mak, 2000 China	NR	NR
Peuskens, 1999 Multi-national, Europe	SARS, AIMS, BAS, proportion of patients receiving antiparkinsonian medication	risperidone vs amisulpride: 23% vs 30% used antiparkinsonians (ns) EPS 12 % vs 14% (ns) Headache 10% vs 11% (ns) Constipation 1% vs 6% (ns) Vomiting 4% vs 5% (ns) Mean weight change +1.4kg vs +0.4kg (p=0.026)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Mak, 2000 China	NR	Patients were not randomly assigned to the two treatment. It they showed significant clinical improvement, they would continue to be maintained with the medication
Peuskens, 1999 Multi-national, Europe	69 total; Due to AEs 14 in risperidone 15 in amisulpride	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Revicki, 1999 Austria, Belgium, Canada, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom, United States (See Tollefson, 1997)	Haloperidol	See Tollefson, 1997 Duration 6 weeks, followed by 1-year blinded extension phase that included responders only. Mean modal dose during acute phase: olanzapine 12.9 mg/day; haloperidol 11.3 mg/day Mean modal dose during extension phase: olanzapine 13.3 mg/day; haloperidol 12.4 mg/day	See Tollefson, 1997	See Tollefson, 1997; Also QLS and SF-36 at baseline and at end of acute phase (6 weeks), then every 8 weeks for patients in the extension phase.
Rosenheck, 1997 Rosenheck, 1999 Rosenheck, 1998 U.S.	haloperidol	clozapine 100-900 mg/day; mean dose at week 26 = 552 mg/day. haloperidol 5-30 mg/day; mean dose at week 26 = 28 mg/day. Weekly blood counts taken in both treatment groups. Duration: 52 weeks.	NR/ NR	PANSS Heinrichs-Carpenter Quality of Life scale (QLS)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Revicki, 1999 Austria, Belgium, Canada, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom, United States (See Tollefson, 1997)	Mean change from baseline score during acute phase, olanzapine vs haloperidol: QLS total: 6.5 vs 3.1 (p=0.005) QLS intrapsychic foundations 2.8 vs 1.0 (p<0.001) QLS interpersonal relations 2.0 vs 0.9 (p=0.036) QLS instrumental role category 1.2 vs 1.0 (ns) QLS common objects and activities 0.5 vs 0.3 (ns) SF-36 summary score, mental component 6.3 vs 2.8 (p<0.001) SF-36 summary score, physical component 0.1 vs -0.2 (ns) Mean change from baseline score to extension phase endpoint: QLS total 13.2 vs 7.1 (p=0.001) QLS intrapsychic foundations 4.7 vs 1.8 (p<0.001) QLS interpersonal relations 4.3 vs 3.0 (ns) QLS instrumental role category 3.2 vs 1.7 (p=0.015) QLS common objects and activities 1.1 vs 0.6 (ns)
Rosenheck, 1997 Rosenheck, 1999 Rosenheck, 1998 U.S.	clozapine vs haloperidol, 20% reduction in score, at timepoint, PANSS (includes crossovers): Week 6: 24% vs 13% (p=0.008) Month 3: 31% vs 25% (ns) Month 6: 26% vs 12% (p=0.001) Month 9: 38% vs 31% (ns) 1 year: 37% vs 32% (ns) QLS: Week 6: 28% vs 28% (ns) Month 3: 39% vs 30% (ns; p=0.06) Month 6: 43% vs 37% (ns) Month 9: 40% vs 42% (ns) 1 year: 48% vs 45% (ns) % change in positive and negative symptoms for clozapine vs haloperidol: At 3 months (includes crossovers; n=366) Positive symptoms: -17.7% vs -13.8%, p=0.03 Negative symptoms: -9.5% vs -2.7%, p=0.03 At 1 year (does not include crossovers; n=235) Positive symptoms: -22.9% vs -16.7%, p=0.02 Negative symptoms: -17.0% vs -8.3%, p=0.09

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Revicki, 1999 Austria, Belgium, Canada, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom, United States (See Tollefson, 1997)	See Tollefson, 1997 Assessments made weekly during acute phase and every 8 weeks during extension phase.	See Tollefson, 1997
Rosenheck, 1997 Rosenheck, 1999 Rosenheck, 1998 U.S.	Barnes Akathisia Scale (BAS), Abnormal Involuntary Movement Scale (AIMS), (Simpson-Angus Scale (SAS), weekly checklist of adverse reactions	clozapine vs haloperidol Tardive dyskinesia mean score, all timepoints: 3.6 vs 5.2 (p=0.005) Akathisia mean score: 2.6 vs 4.0 (p<0.001) EPS: 2.6 vs 4.0 (p<0.001) AEs: Leukopenia in 4 clozapine and 2 haloperidol patients. Neutropenia in 8 clozapine and 9 haloperidol patients. Agranulocytosis in 3 clozapine patients.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Revicki, 1999 Austria, Belgium, Canada, France, Germany, Italy, Poland, Portugal, Spain, United Kingdom, United States (See Tollefson, 1997)	See Tollefson, 1997	Outcome: quality of life
Rosenheck, 1997 Rosenheck, 1999 Rosenheck, 1998 U.S.	245 total; Due to AEs: 26 in clozapine, 27 in haloperidol clozapine vs haloperidol discontinuations (no p-values given) due to lack of efficacy/worsening of symptoms: 15% vs 51% due to side effects: 30% vs 17% due to non-drug-related reasons: 55% vs 32% At 3 months, 81% of clozapine patients vs 73% of haloperidol patients (p<0.05) were continuing study drug by 1 year, 60% of clozapine patients vs 28% of haloperidol patients (p<0.0001) continued study medication	Patients with refractory schizophrenia, high levels of hospitalization

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Rosenheck, 2003 U.S.	haloperidol	olanzapine 5-20 mg/day, mean dose 15.8 mg/day during last 6 months; given with placebo benztropine. haloperidol 5-20 mg/day, mean dose 14.3 during last 6 months; given with benztropine mesylate 1-4 mg/day. Duration 12 months	NR/ NR	PANSS, QLS at baseline, 6 weeks, and 3, 6, 9, and 12 months Neurocognitive status (RBANS, Grooved Pegboard, Wisconsin Card Sorting Test-64 Card Version, Trail-making test part B, Controlled Oral Word Association Test, Wide Range Achievement Test-Revised) at baseline and 3, 6, and 12 months
Rubio, 2006 RCT, open, crossover Spain	zuclopenthixol	risperidone: mean dose 6.4 mg/d (range 3-12) zuclopenthixol: mean dose 38 mg/d (range 10-100) Duration: 6 months (6 months and crossover for 6 more months)	No	PANSS, CGI, ASI Weekly urine tests for substance abuse, reactive strips for alcohol, cocaine, opiates and cannabis
Sayers, 2005 U.S.	haloperidol	olanzapine 10 mg or haloperidol 10 mg, up to 20 mg for each and the current antipsychotic medications were halved. Patients were tapered from their previous antipsychotic medication over the first 1 to 2 weeks.	No	Weekly - cocaine use and the amount of craving were captured through urine drug screens that assessed semiquantitative benzoylecgonine levels (>300 nanograms per milliliter), and a visual analogue scale (VAS) to assess patients' self-reported level of craving for cocaine.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Rosenheck, 2003 U.S.	Mean scores not provided; graphs and statistical significance only. No between-group differences in PANSS total, PANSS positive, or PANSS negative subscales, QLS, SF-36, or CG Outcomes scale. No differences at any time point in proportion of patients with 20% improvement in PANSS scores. Neurocognitive tests: Significantly greater improvement in olanzapine on motor functioning (p=0.02) and memory (p=0.03) but not on Wisconsin Card Sorting test (ns).
Rubio, 2006 RCT, open, crossover Spain	Outcomes for first period (prior to crossover), mean, SD (risperidone vs. zuclopenthixol) PANSS-total: 66.81 (21.34) vs. 73.68 (21.1) PANSS-positive: 13.23 (4.20) vs. 14.42 (5.18) PANSS-negative: 18.8 (5.31) vs. 22.97 (7.40) PANSS-general: 34.7 (9.26) vs. 36.32 (11.92) Substance abuse Tests performed during study period: 19.76 (3.6) vs. 17.55 (4.3) Total positive tests during study period: 8.67 (3.0) vs. 10.31 (3.1) >/= 20% total PANSS reduction: 57.6% vs. 48.5%
Sayers, 2005 U.S.	There were no significant differences overall in proportions of positive drug screens between treatment groups; no differences in positive, negative, or depressive symptoms; and few differences between treatment conditions in extrapyramidal symptoms. However, craving for cocaine was rated significantly lower by patients treated with haloperidol compared with patients treated with olanzapine. (P < 0.05)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Rosenheck, 2003 U.S.	BAS, AIMS, SARS, CGI, SF-36 checklist of adverse reactions, at baseline, 6 weeks, 3, 6, 9, and 12 months. Neurocognitive status at baseline and at 3, 6, and 12 months: RBANS, Grooved Pegboard, Wisconsin Card Sorting Test-64 Card Version, Trail-Making Test Part B, Controlled Oral Word Association Test, Wide Range Achievement Test-Revised	olanzapine vs haloperidol: BAS: significantly lower scores in olanzapine (p<0.001) AIMS: no between-group differences Patient reports of weight gain at 6 months 32.5% vs 12.5% (p=0.002); at 12 months 24.7% vs 8.3% (p=0.01) Restlessness* at 6 months 15.1% vs 28.0% (p=0.04); at 12 months 15.2% vs 28.0% (p=0.06)
Rubio, 2006 RCT, open, crossover Spain	ESRS, UKU	ESRS (risperidone vs. zuclopenthixol) 1.94 (0.6) vs. 2.85 (1.11) More significant reduction in scores on the scales for EPS and UKU in risperidone group (t=1.92, P=0.04) Antiparkinsonian drugs used more frequently in zuclopenthixol group (48.5% vs. 27%, chi2=3.23, df=1, P=0.07)
Sayers, 2005 U.S.	The timeline follow-back method was used to assess cocaine use prior to the beginning of the study. Monthly ratings were used to measure EPS, including the AIMS, the BAS, and the SARS.	NR

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Rosenheck, 2003 U.S.	132 total; Due to AEs: 15 in olanzapine vs 6 in haloperidol	
Rubio, 2006 RCT, open, crossover Spain	Total withdrawals: 4 risperidone: 1 zuclopenthixol: 3 Withdrawals due to AEs: 0	No washout period. I've reported results for 1st 6 month period and not post-crossever results
Sayers, 2005 U.S.	Total withdrawals 42% (10) Withdrawals due to Aes - NR	This study is pretty bad

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Sechter, 2002 Austria, Belgium, Estonia, France, Germany, Hungary, Latvia, The Netherlands, Slovenia	amisulpride	risperidone 4-10 mg/day amisulpride 400-1000 mg/day Duration 6 months	6-day single-blind placebo washout	PANSS and CGI at weeks 1,2,3,4,6,8 and at 3, 4, 5, and 6 months; PANSS also at washout SANS, BRMS, SOFAS at baseline, week 8, and 6 months Subjective response scale at week 1 and 8, and 6 months
Shopsin, 1979 U.S.	chlorpromazine	clozapine 300-800 mg/day chlorpromazine hydrochloride 600-1600 mg/day Duration: 35 days	NR/ 3-7 days	BPRS, CGI, Nurses' Observation Scale for Inpatient Evaluation (NOSIE)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Sechter, 2002 Austria, Belgium, Estonia, France, Germany, Hungary, Latvia, The Netherlands, Slovenia	risperidone vs amisulpride, efficacy: Mean change in score from baseline to 6 months PANSS total -31.4 vs -32.2 (ns) PANSS positive subscale -12.1 vs -11.8 (ns) PANSS negative subscale -3.9 vs -5.1 (ns) PANSS global psychopathology -15.4 vs -15.3 (ns) BPRS total -19.6 vs -19.8 (ns) CGI severity -1.5 vs -1.7 (ns) SANS -12.1 vs -14.8 (ns) BRMS -3.9 vs -4.9 (ns) Patients with PANSS >= 50% improvement: 52.0% vs 65.3% (p=0.036) Patients with BPRS >=50% improvement: 57.7% vs 71.9% (p=0.020) Patients with CGI very much or much improved: 65.0% vs 76.9% (p=0.042) risperidone vs amisulpride, safety: Mean change in score from baseline to 6 months SARS 0.07 vs 0.10 (ns) AIMS 0.10 vs 0.16 (ns)
Shopsin, 1979 U.S.	BPRS 18 items, n/18 items with p<0.05 vs baseline clozapine: 15/18 chlorpromazine: 6/18 BPRS 6 factors, n/6 factors with p<0.05 vs baseline clozapine: 6/6 chlorpromazine: 2/6 (thought disturbance and activation) placebo: 2/6 (activation and hostility suspiciousness) NOSIE: social competence, social interest, personal neatness, irritability, magifest psychosis, retardation, total patient assets, global severity clozapine and chlorpromazine both more improved than placebo, p<0.05 CGI global severity: clozapine and chlorpromazine both more improved than placebo, p<0.05 total Psychiatrics (CGI) improved: clozapine vs chlorpromazine: 90% vs 75% NOSIE (CGI) total improved: clozapine vs chlorpromazine: 100% vs 75%

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Sechter, 2002 Austria, Belgium, Estonia, France, Germany, Hungary, Latvia, The Netherlands, Slovenia	Physical exam, vital signs, body weight, SARS and BAS at washout, baseline, and weeks 1,2,3,4,6,8 AIMS at washout, baseline, week 8, and 6 months	Weight gain >=7% from baseline to 6 months: 34% risperidone vs 18% amisulpride (p<0.05) Antiparkinsonian medication taken at least once by 30% on risperidone and 24% on amisulpride (ns)
Shopsin, 1979 U.S.	modified Simpson-Angus Scale	antiparkinsonism medication for EPSs (no. of patients): clozapine vs chlorpromazine: 0 vs 5 Hypersalivation: clozapine vs chlorpromazine: 11(85%) vs 1(8%) Sedative effect: NR, NS daytime drowsiness: chlorpromazine more than clozapine, NR

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Sechter, 2002 Austria, Belgium, Estonia, France, Germany, Hungary, Latvia, The Netherlands, Slovenia	123 total; Due to AEs: 20 in risperidone, 21 in amisulpride	
Shopsin, 1979 U.S.	NR	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Shrivastava, 2000 India	haloperidol	risperidone 2 mg/day haloperidol: 5-15 mg/day Duration: 1 year	2-4 weeks with haloperidol 15-30 mg/day / NR	PANSS CGI
Silva de Lima, 2005 RCT, open label, multicenter Brazil	first generation antipsychotics (FGAs)	olanzapine mean (SD): 10.5 mg/d (2.5 mg/d) FGAs haloperidol (n=74): 15.8 mg/d (23.7 mg/d) chlorpromazine (n=13): 346.2 mg/d (150.6 mg/d) trifluoperazine (n=1): 15 mg/d	NR	SF-36 at monthly intervals for 9 months following discharge from hospital
Smelson, 2006 U.S.	haloperidol	olanzapine (n=16) haloperidol (n=15) Study physician used same dosing schedule for both drugs: 5 mg/d for first 4 days, increased by 5 mg/d every 4 days to maximum dose of 20 mg/d by day 12 and target dose of 10 mg/d	No	Voris Cocaine Craving Scale (VCCQ), PANSS General Psychopathology Subscale

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Shrivastava, 2000 India	riesperidone vs haloperidol, change from baseline (SD), % reduction, p value PANSS: positive: 11.2(4.2), 55.5% vs 10(3.0), 47.6%, NS negative: 18.3(4.0), 58.8% vs 15.0(3.5), 51.2%, NS general psychopathology: 20.4(4.9), 50.5% vs 27(3.7), 68.4%, p<0.05 total: 50.4(5.7), 57.8% vs 52(4.1), 58.4%, NS CGI (improved) overall very much improvement (no. of patients): 18 vs 5, p<0.05 social functioning: 34 vs 22, p<0.02 productivity: 35 vs 18, p<0.001 economic independence: 31 vs 29, NS education: 40 vs 25, p<0.003 suicidality: 5 vs 17, p<0.009 rehospitalization: 6 vs 15, p<0.05 exacerbation: 7 vs 6, NS
Silva de Lima, 2005 RCT, open label, multicenter Brazil	SGA score at endpoint olanzapine vs. FGAs, mean difference; CI, P-value (based on LOCF) Physical functioning: 82.3 vs. 73.8, 6.6; CI: 1.2 to 11.9, P=0.017 Role physical: 58.1 vs. 40.0, 13.7; CI: 3.0 to 24.3, P=0.023 Bodily pain: 86.0 vs. 79.1, 6.1; CI: -1.5 to 13.8, P=0.12 General health: 67.0 vs. 61.1, 5.6; CI: 0.0 to 11.3, P=0.05 Vitality: 56.3 vs. 51.0, 0.4; CI: -5.1 to 5.9, P=0.9 Social functioning: 72.2 vs. 67.1, 5.4; CI: -2.3 to 13.2, P=0.17 Role emotional: 58.4 vs. 42.1, 12.1; CI: 0.7 to 23.5, P=0.04 Mental health: 64.0 vs. 58.1, 5.1; CI: -0.3 to 10.4, P=0.06
Smelson, 2006 U.S.	Olanzapine subjects showed significantly less cue-elicited craving on VCCQ Energy score vs. haloperidol subjects (M=39.1, SD=9.2 vs. M=27.6, SD=12.8), t(16)=2.20, P=0.04 (2-tailed), d=0.99, but not on the Intensity (M=8.5, SD=5.7 vs. M =14.4, SD=11.8), t(16)=1.39, P=0.18 (2-tailed), d=0.64; Mood (M=37.1, SD=12.0 vs. M=28.9, SD=16.2), t(16)=-1.23, P=0.23 (2-tailed), d=0.58; and Sick (M=39.7, SD=11.6 vs. M=28.5, SD=17.4), t(16)=-1.64, P=0.12 (2-tailed), d=0.78, dimensions of craving 12.5% of olanzapine patients had positive urine toxicology screening for an illicit substance at some point over course of study compared with 40% of haloperidol patients, P=0.20 PANSS Olanzapine subjects compared with haloperidol subjects received lower score approaching statistical significance on PANSS General Psychopathology Subscale (M=41.6, SD=6.1 vs. M=47.7, SD=7.5), t(16)=1.88, P=0.07 (2-tailed), d=0.89. Differences between groups on the PANSS Positive Subscale (M=18.3, SD=3.9 vs. M=20.3, SD=4.1), t(16)=1.01, P=0.33 (2-tailed), d=0.50, and PANSS Negative Score (M=19.0, SD=3.5 vs. M=22.2, SD=4.5), t(16)=1.68, P=0.11 (2-tailed), d=0.79, were not significant.

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Shrivastava, 2000 India	NR	NR
Silva de Lima, 2005 RCT, open label, multicenter Brazil	Adverse events recorded at every visit, including entry (visit 0) through nondirected, open-ended questioning, spontaneous complaint, and clinical observation; and AIMS	AIMS olanzapine vs. FGAs, RR (95% CI), p-value Tardive dyskinesia: 11.5% vs. 38.9%, 0.4 (0.2 to 0.7), P<0.001 Incapacitation: 23.0% vs. 47.2%, 0.6 (0.4 to 0.8), P=0.001 Patient awareness: 18.4% vs. 34.7%, 0.6 (0.4 to 1.0), P=0.015 Choreoathetosis: 0.0% vs. 12.5%, [RR & CI not available], P=0.001 Dystonia: 5.7% vs. 20.8%, 0.4 (0.2 to 0.9), P=0.004 Olanzapine patients gained significantly more weight than FGA patients with a correspondent endpoint increase in BMI of 28.7 vs. 25.3 (P<0.001)
Smelson, 2006 U.S.	NR	NR

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Shrivastava, 2000 India	NR	
Silva de Lima, 2005 RCT, open label, multicenter Brazil	Total withdrawals: 26 (13.2%) olanzapine: 13 (12.5%) FGAs: 13 (14%) Due to AEs: olanzapine: 1 (1.0%) FGAs: 0 (0.0%)	For efficacy, I just reported QoL outcomes per Sujata's instructions
Smelson, 2006 U.S.	Total withdrawals: 13 (41.9%) olanzapine: 8 (50%) haloperidol: 5 (33.3%) Due to AEs: NR	Completer's analysis only; high attrition

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Tran-Johnson, 2007 Multinational	haloperidol	IM aripiprazole 1 mg, 5.25 mg, 9.75 mg and 15 mg , IM haloperidol 7.5 mg, or IM placebo Duration: 24 hours	No	Mean improvement in PEC (five items on the PANSS total scale (hostility, lack of cooperation, excitement, poor impulse control, and tension) CGI-S, CGI-I, ACES, BPRS and CABS at 2 hours
Tunis 2006 U.S.	Conventionals	1) olanzapine as first-line treatment (OLZ); versus 2) first-line treatment with a maximum of two (consecutive) conventional agents before a possible switch to olanzapine (CON); and versus 3)risperidone as first-line treatment (RIS).	No	BPRS and Lehman Quality of Life Interview (LQLI)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Tran-Johnson, 2007 Multinational	Placebo vs. IM aripiprazole 1 mg vs. 5.25 mg vs. 9.75 mg vs. 15 mg vs. IM haloperidol 7.5 mg at 2 hours Change in ACES 0.66 vs. 0.65 vs. 1.01 vs. 1.50** vs. 0.99 vs. 1.50** Change in CABS -2.95 vs. -5.16 vs. -5.97** vs. -7.08*** vs. -7.04*** vs. -8.13*** Change in CGI-S -0.42 vs.-0.63 vs.-0.82* vs. -1.08*** vs. -0.99** vs. -0.91* CGI-I 3.46 vs. 3.07* vs. 2.82*** vs. 2.64*** vs. 2.66*** vs. 2.72*** * P < 0.5 vs. placebo ** P < 0.01 vs. placebo *** P < 0.001 vs. placebo PEC scores were significantly better in the IM aripiprazole 5.25 mg, 9.75 mg and 15 mg and IM haloperidol 7.5 mg vs. placebo (all P < 0.01) (not the 1 mg arpiprazole) (results presented graphically)
Tunis 2006 U.S.	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Tran-Johnson, 2007 Multinational	Patient and investigator reported; EPS via SAS and BAS; lab tests included 12 lead ECGs and vital signs Adverse events coded with MedDRA	Placebo vs. IM aripiprazole 1 mg vs. 5.25 mg vs. 9.75 mg vs. 15 mg vs. IM haloperidol 7.5 mg % Reporting at least 1 29.5 vs. 50.0 vs. 48.4 vs. 44.6 vs. 46.6 vs. 49.1 Tachycardia 1.6 vs. 5.4 vs. 3.2 vs. 7.1 vs. 0 vs. 1.8 Sinus tachycardia 1.6 vs. 1.8 vs. 0 vs.0 vs. 0 vs. 5.3 Vomiting 1.6 vs. 1.8 vs. 0 vs. 3.6 vs. 5.2 vs. 1.8 Nausea 3.3 vs. 0 vs. 9.7 vs. 10.7 vs. 3.4 vs. 1.8 Dizziness 6.6 vs. 7.1 vs. 11.3 vs. 7.1 vs. 12.1 vs. 7.0 Headache 1.6 vs. 7.1 vs. 17.7 vs. 10.7 vs. 13.8 vs. 3.5 Somnolence 4.9 vs. 5.4 vs. 8.1 vs. 5.4 vs. 10.3 vs. 12.3 Akathisia 0 vs. 0 vs. 3.2 vs. 35.4 vs. 0 vs. 10.5 Dystonia 0 vs. 0 vs. 0 vs. 1.8 vs. 1.7 vs. 7.0 Agitation 1.6 vs. 0 vs. 0 vs. 3.6 vs. 5.2 vs. 1.8
Tunis 2006 U.S.	Treatment-emergent Aes using CoSTART, development of extrapyramidal symptoms (EPS) using SAS and BAS, and changes in weight.	Patients experiencing a SAE - CON 17.3%, OLZ 19.7%, RIS 19.0% Weight gain CON patients (n = 67) gained 2.43 kg, compared with 6.00 kg for OLZ (n = 125) and 3.19 kg for RIS (n = 99).

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Tran-Johnson, 2007 Multinational	19 withdrawals 2 due to AE	
Tunis 2006 U.S.	Withdrawals 209 Due to Aes: NR	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Tollefson, 1997 Breier, 1999 Gilmore, 2002 Glick, 2002 Goldstein, 2002 Gomez, 2001 Hamilton, 2000 Kennedy, 2003 Kinon, 2001 Revicki, 1999 Sanger, 1999 Tohen, 2001 Tran, 1999 Tollefson, 1998 Tollefson, 1999 Tunis, 1999 174 sites in 17 countries	haloperidol	olanzapine 5-20 mg/day; mean dose 13.2 mg/day haloperidol 5-20 mg/day; mean dose 11.8 mg/day Duration 6 weeks	2-9 day washout	Weekly assessments of efficacy: PANSS, CGI, BPRS extracted from PANSS, MADRS, QLS, SF36, prolactin
Tran, 1999 (See Tollefson, 1997)	Haloperidol	See Tollefson, 1997 Duration 6 weeks, followed by 1-year blinded extension phase that included responders only. Mean modal dose during acute phase: olanzapine 11.5 mg/day; haloperidol 10 mg/day. Mean modal dose during extension phase: olanzapine 12.9 mg/day; haloperidol 13.8 mg/day.	See Tollefson, 1997	See Tollefson, 1997

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Tollefson, 1997	Change in mean score from baseline to acute phase endpoint, olanzapine vs haloperidol:
Breier, 1999	BPRS total -10.9 vs -7.9 (p<0.02)
Gilmore, 2002	PANSS total -17.7 vs -13.4 (p=0.05)
Glick, 2002	PANSS positive -4.7 vs -3.8 (ns)
Goldstein, 2002	PANSS negative -4.5 vs -3.2 (p=0.03)
Gomez, 2001	CGI severity -1.0 vs -0.7 (p<0.03)
Hamilton, 2000	MADRS -6.0 vs -3.1 (p=0.001)
Kennedy, 2003	
Kinon, 2001	
Revicki, 1999	
Sanger, 1999	
Tohen, 2001	
Tran, 1999	
Tollefson, 1998	
Tollefson, 1999	
Tunis, 1999	
174 sites in 17 countries	
Tran, 1999	Change in mean score at acute phase and extension phase endpoints, olanzapine vs haloperidol:
(See Tollefson, 1997)	All schizoaffective patients
	Acute BPRS total -10.52 vs -5.50 (p=0.002)
	Acute PANSS total -17.05 vs -9.06 (p=0.003)
	Acute PANSS positive -4.11 vs -2.49 (ns)
	Acute PANSS negative -4.16 vs -2.07 (p=0.006)
	Acute MADRS total -7.39 vs -0.79 (p<0.001)
	Extension BPRS total -15.96 vs -14.44 (ns)
	Extension PANSS total -26.80 vs -24.68 (ns)
	Extension PANSS positive -7.21 vs -7.72 (ns)
	Extension PANSS negative -6.25 vs -5.08 (ns)
	Extension MADRS total -8.26 vs -3.32 (p=0.045)
	Bipolar type
	Acute BPRS total -10.60 vs -5.86 (p=0.012)
	Acute PANSS total -16.82 vs -9.96 (p=0.028)
	Acute PANSS positive -4.27 vs -2.73 (ns)
	Acute PANSS negative -3.97 vs -2.02 (p=0.031)
	Acute MADRS total -6.93 vs -0.17 (p<0.001)
	Extension BPRS total -16.29 vs -14.56 (ns)
	Extension PANSS total -26.53 vs -25.44 (ns)
	Extension PANSS positive -7.60 vs -7.81 (ns)
	Extension PANSS negative -6.04 vs -4.69 (ns)
	Extension MADRS total -6.36 vs -3.69 (ns)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Tollefson, 1997 Breier, 1999 Gilmore, 2002 Glick, 2002 Goldstein, 2002 Gomez, 2001 Hamilton, 2000 Kennedy, 2003 Kinon, 2001 Revicki, 1999 Sanger, 1999 Tohen, 2001 Tran, 1999 Tollefson, 1998 Tollefson, 1999 Tunis, 1999 174 sites in 17 countries	Clinical report form records, AMDP-5, vital signs, SARS, BAS, laboratory tests, ECGs, ophthalmological examinations, and chest X-rays. Weekly assessments of safety: EPS, SAS, BAS, AIMS.	EPS and sleep disruptions, several anticholinergic effects, and hypersalivation significantly more frequent in haloperidol than olanzapine. olanzapine vs haloperidol (p<0.05): Excessive appetite 24.0% vs 12.4% Dry mouth 22.2% vs 16.2% Interrupted sleep 19.0% vs 30.3% Shortened sleep 15.1% vs 24.8% Drowsiness 26.0% vs 31.3% Hypertonia 8.4% vs 21.1% Tremor 16.5% vs 26.3% Acute dyskinesia 2.8% vs 8.0% Hypokinesia 5.1% vs 13.5% Akathisia 14.2% vs 35.5% Estimated % of patients discontinued at 12 months: 37% vs 47% Estimated mean time to discontinuation (day): 271 vs 241 Relapse rates at 52 weeks among responders: 34% vs 37%, p=0.466
Tran, 1999 (See Tollefson, 1997)	As in Tollefson, 1997; also AIMS. Elicited by investigator and reported spontaneously by patient.	olanzapine vs haloperidol, Mean change in acute phase: Weight: +1.49 kg vs -0.24 kg (p=0.0001). EPS scores (SAS LOCF): -0.85 vs +1.65 (p=0.001) BAS: -0.18 vs +0.81 (p<0.001) Proportion who experienced akathisia: 16.6% vs 52.3% (p<0.001) Proportion who experienced pseudoparkinsonism: 9.8% vs 37.2% (p<0.001) Mean change in extension phase: Weight: +5.02 vs -1.53 (p=0.002) SAS total scores: -1.34 vs +0.88 (p=0.016) BAS: -0.24 vs +0.16 (ns) Proportion who experienced pseudoparkinsonism: 4.5% vs 9.2% (p<0.001) Proportion who experienced akathisia: 18.4% vs 52.4% (p=0.002)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Tollefson, 1997 Breier, 1999 Gilmore, 2002 Glick, 2002 Goldstein, 2002 Gomez, 2001 Hamilton, 2000 Kennedy, 2003 Kinon, 2001 Revicki, 1999 Sanger, 1999 Tohen, 2001 Tran, 1999 Tollefson, 1998 Tollefson, 1999 Tunis, 1999 174 sites in 17 countries	799 total; Due to AEs: 60 (4.5%) in olanzapine 48 (7.3%) in haloperidol (p=0.01)	
Tran, 1999 (See Tollefson, 1997)	Acute phase: 157 withdrawals. Due to AEs: 15 (7.7%) in olanzapine, 10 (9.6) in haloperidol (ns) Extension phase: 56 withdrawals. Due to AEs: 15 (17.6%) in olanzapine, 6 (24.0%) in haloperidol (ns)	Subpopulation of Tollefson 1997: schizoaffective

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Vanelle, 2006 RCT, DB Multicenter, multinational	amisulpride	amisulpride: 200-600 mg/d olanzapine: 5-15 mg/d Duration: 8 weeks	Single blind placebo washout period of 3-6 days	Primary efficacy measures: CDS total score (change from baseline) CGI item 2 proportion of responders Secondary efficacy measures: PANSS total, positive, negative and general psychopathology scores CGI BPRS score and BPRS factor scores Time to premature treatment discontinuation Weeks 1, 2, 4, 6, and 8

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Vanelle, 2006 RCT, DB Multicenter, multinational	Primary outcome measures (amisulpride vs. olanzapine) CDS Baseline: 12.80 (4.06) vs. 5.95 (4.06) Endpoint: 11.46 (3.36) vs. 4.10 (4.10) Mean change: -6.84 (4.42) vs. -7.36 (3.91); P=0.20 CGI responders Much improved or very much improved: 65.9% vs.. 61.5%; p=0.68 Secondary outcome measures, change from baseline (amisulpride vs. olanzapine) PANSS scale Total score: -14.89 (14.78) vs. -17.82 (12.47); P=0.2340 Positive score: -2.32 (4.14) vs. -3.31 (3.15); P=0.3262 Negative score: -3.30 (3.63) vs. -3.56 (3.10); P=0.4915 General psychopathology: -9.27 (8.88) vs. -10.95 (7.84); P=0.2066 BPRS Total score: -10.09 (9.07) vs. -11.49 (7.54); P=0.2266 Anxiety-depression: -4.43 (3.18) vs. -5.03 (2.63); P=0.0745 Anergia: -2.30 (1.96) vs. -1.87 (1.76); P=0.8300 Thought disturbance: -1.43 (2.28) vs.-1.31 (2.00); P=0.9780 Activation: -1.07 (1.62) vs. -1.59 (1.52); P=0.1191 Hostile-suspiciousness: -0.88 (2.79) vs. -1.69 (2.02); P=0.3331 CGI Item 1: severity: -1.34 (1.14) vs. -1.51 (1.10); P=0.5416 Item 3: efficacy index: 2.58 (1.19) vs. 2.91 (1.04); P=0.2155 Premature treatment discontinuation (days): 51.57 (13.27) vs. 54.03 (10.61); P=0.1122

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Vanelle, 2006 RCT, DB Multicenter, multinational	Solicited AE reporting, tests of neurological status, routine lab tests (including fasting blood glucose, cholesterol, HDL and triglycerides), ECG monitoring, and body weight	Adverse events reported (amisulpride vs. olanzapine) Anxiety: 6.7% vs. 5.0% Tremor: 6.7% vs. 0 Headache: 4.4% vs. 5.0% Hypertriglyceridaemia: 2.2% vs. 10.0% Weight increase: 2.2% vs. 7.5% Nausea: 6.7% vs. 0 At least 1 AE reported: 53.3% vs. 47.5%; P=0.59 Weight increase >/= 7% at endpoint: 8.9% vs. 15%; P=0.51 No significant change in frequency or intensity of EPS in either group during study Scores on SAS, Barnes Akithisia Index and AIMS not significantly different between groups at endpoint

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Vanelle, 2006 RCT, DB Multicenter, multinational	Total withdrawals: 14 Withdrawals due to AEs: 2 amisulpride: 2 olanzapine: 0 2 postrandomization exclusions (1 in each group); ITT population=83	

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Other drug	Interventions	Run-in/ Washout period	Method of outcome assessment and timing of assessment
Wright, 2003 Wright, 2001 Australia, Austria, Belgium, Canada, the Czech Republic, France, Greece, Hungary, Israel, Republic of South Africa, Spain, United Kingdom, United States	haloperidol	IM olanzapine 10mg IM haloperidol 7.5mg the 24-hour IM period was followed by 4 days PO treatment with olanzapine or haloperidol tablets (5-20 mg/day for both)	NR/ NR	PANSS-EC

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Results
Wright, 2003 Wright, 2001 Australia, Austria, Belgium, Canada, the Czech Republic, France, Greece, Hungary, Israel, Republic of South Africa, Spain, United Kingdom, United States	Mean change at 24 hours from baseline, p value vs placebo BPRS positive: placebo: -1.3(2.7) olanzapine: -2.8(3.1), p<0.001 haloperidol: -3.2(3.5), p<0.001 BPRS total: placebo: -6.2(9.0) olanzapine: -12.8(9.0), p<0.001 haloperidol: 12.9(8.9), p<0.001 CGI-I: placebo: -0.1(0.6) olanzapine: -0.5(0.8), p<0.05 haloperidol: -0.8(0.8), p<0.05 PANSS: placebo: -3.1(5.1) olanzapine: -6.5(5.3), p<0.001 haloperidol: -6.7(4.6), p<0.001 olanzapine vs haloperidol, p=0.76 Agitated Behavior Scale score: placebo: -3.7(6.7) olanzapine: -6.4(5.9), p=0.003 haloperidol: -6.6(5.3), p=0.002 olanzapine vs haloperidol, p=0.91 Agigated Calmness Evaluation Scale score: placebo: 0.6(1.2) olanzapine: 0.8(1.0), p=0.2 haloperidol: 1.1(1.0), p=0.002 olanzapine vs haloperidol, p=0.02 Response rate: placebo: 18(33.3%) olanzapine: 96(73.3%), p<0.001 haloperidol: 87(69%), p<0.001 olanzapine vs haloperidol, NS Mean change at PO endpoint from baseline, all NS between groups PANSS-EC: olanzapine: -0.6(4.8) haloperidol: -1.3(4.4)

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Method of adverse effects assessment?	Adverse effects reported
Wright, 2003 Wright, 2001 Australia, Austria, Belgium, Canada, the Czech Republic, France, Greece, Hungary, Israel, Republic of South Africa, Spain, United Kingdom, United States	Spontaneously reported EPS: Barnes Akathisia Scale (BAS) and Simpson-Angus Scale (SAS)	Mean change at 24 hours from baseline, p value vs IM haloperidol Simpson-Angus Scale (SAS): olanzapine: -0.61(2.26), p<0.001 haloperidol: 0.70(3.54), NA placebo: -1.19(3.32), NR Barnes Akathisia Scale (BAS): olanzapine: -0.27(0.73), p<0.05 haloperidol: 0.01(0.77), NA placebo: -0.08(0.79), NR Mean change at PO endpoint from baseline, all NS between groups SAS: olanzapine: -0.24(1.51) haloperidol: 0.14(3.28) BAS: olanzapine: 0.00(0.63) haloperidol: 0.09(0.87) Dystonia: olanzapine: 0(0%) haloperidol: 1(0.8%) olanzapine vs haloperidol, p=0.001 EPS: olanzapine: 1(0.8%) haloperidol: 7(5.6%) olanzapine vs haloperidol, p=0.03

Evidence Table 4. Active-controlled trials in patients with schizophrenia

Author, year Country (Trial name)	Total withdrawals; withdrawals due to adverse events by drug	Comments
Wright, 2003 Wright, 2001 Australia, Austria, Belgium, Canada, the Czech Republic, France, Greece, Hungary, Israel, Republic of South Africa, Spain, United Kingdom, United States	Olanzapine vs haloperidol Total withdrawals: 10 vs 10 Withdrawals due to AEs: 2 vs 2	

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
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: anticholinergicvs, lorazepam for agitation and temazepam (upper limit=20mg) for insomnia
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 antispychotics not allowed; anticholinergics were titrated according to the EPS, and benzodiazepines could be prescribed adjunctively if the patients psychiatric condition was unstable.
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

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

Author, year Country Trial name	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Arato, 2002 Europe Inpatients	Mean age: 49.7 years Age range: 20-82 years 73% male Ethnicity: NR	Smokers: 68.7%	329/ 294/ 278	179/ NR / 277
Bai, 2003 Taiwan Inpatients	Mean age: 50.2 years 66.7% male Ethnicity: NR	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
Baker, 1996 United States Inpatients	Mean age: 36 years 68% male Ethnicity: NR	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

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

Author, year Country Trial name	Outcome scales	Method of outcome assessment and timing of assessment
Arato, 2002 Europe Inpatients	PANSS CGI GAF	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	BPRS	Baseline and endpoint mental status assessed with BPRS.
Baker, 1996 United States Inpatients	see "methods of outcome assessment..." column	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
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
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

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

Author, year Country Trial name	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Beasley, 2003 Beasley, 2006 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	Mean age 36 (SD 11) 53% male Ethnicity not reported	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
Borison, 1996 United States	Mean age = 36 (18-58) years Gender: 91% male Ethnicity: 62% white; 36% black; 3% other	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

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

Author, year Country Trial name	Outcome scales	Method of outcome assessment and timing of assessment
Beasley, 2003 Beasley, 2006 Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	BPRS, PANSS, Heinrichs-Carpenter Quality of Life Questionnaire	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	Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression (CGI) Modified Scale for the Assessment of Negative Symptoms (SANS)	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	Patients relapsing after 8 weeks of maintenance
Beasley, 2006	olanzapine: 9/224 (4.0%) vs placebo: 28/102 (27%), p<0.001
Croatia, Poland, Romania, the Russian Federation, US, Yugoslavia Olanzapine Relapse Prevention Study	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
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 schizopheina 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 antipsycotic 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
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	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.
Cutler, 2006 United States	apripiprazole 2mg/day apripiprazole 5mg/day apripiprazole 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 apripiprazole prohibited with the exception of lorazepam (max 4mg/day = amizety or emergent agitation not w/in 4hr of safety or efficacy assesment), However zolipdem and zaleplon (non benzodiazepine medications) were allowed for insomnia. Additionally anticholinergic medications were permittted for EPS treatment but not 24 hours prior to randomization or within 12 hours of safety and efficacy rating assessment .
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), benzotropine (for EPS) , and beta-andrenoceptor antagonists (for akathisia) were allowed if required but were not administered prophylactically.

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

Author, year Country Trial name	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Ciliberto, 2005 (see Kane 2003)	Age Caucasian 39.0 African-American 38.0 Other 35.9 Gender Caucasian 72.5% African-American 68.4% Other 76.4	Diagnosis (%) Scizophrenia 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	NR/ NR/ 429
Cutler, 2006 United States	Mean age: 41.1 years 78.5% male 21.5% female 48.1% white 47% black/ african american 4.9% Other	Mean baseline PANSS total score: 90.9	NR/367/367	80/NR/195
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	Mean age: Age range: 18-67 years 71.2% male 68.2% white 19.9% black 2.3% Asian 9.6% other	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

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

Author, year Country Trial name	Outcome scales	Method of outcome assessment and timing of assessment
Ciliberto, 2005 (see Kane 2003)	CGI-S PANSS	PANSS every 2 weeks, CGI every week.
Cutler, 2006 United States	PANSS total score, PEC Scores PANSS positive and negative factor scores, CGI scale.	Primary efficacy outcome measure was themean 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 ofthe study(-11.3 vs -5 p=.030)
Daniel, 1999 United States and Canada Inpatients (mandatory hospitalization for the first two weeks of treatment)	PANSS, total and negative subscale scores MADRS BPRSd, total core items scores CGI-S CGI-I	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 PASS Active vs. Placebo Caucasian -7.8 vs. 0.8 African-American -11.5 vs. -6.1 Other -12.0 vs. 8.3 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: Apripirazole 10mg/day, patients improved from baseline for PANSS total at endpoint (-11.3 vs -5.3; P=0.3). At weeks 2-5 aripirazole 5mg/day no greater improvement in PANSS total. Apripiprazole 2mg/day no statistically significant imporvements.
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	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.
Inpatients (mandatory hospitalization for the first two weeks of treatment)	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 treament 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 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 benzotropine: 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 (ie. 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
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 hydtate, zaleplon and zopiclone. Also lorazepam and oxazepam during 1st 6 days
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.

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

Author, year Country Trial name	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Kahn, 2007 Multinational	Mean age 34 years Gender- 60.2% male Ethnicity 59.2% white, 4.5% black, 36.1% Asian < 1% other	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	NR/NR/588	112/7/573
Kane, 2003 Nasrallah, 2004 United States	Mean age 38 (SD 10) 75% male 42% African American, 42% white, 11% Hispanic, 6% other ethnicity	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

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

Author, year Country Trial name	Outcome scales	Method of outcome assessment and timing of assessment
Kahn, 2007 Multinational	Clinical Global Impression (CGI) Negative Scale of the Positive and Negative Syndrome Scale (PANSS)	PANNS and CGI-S wekly and CGI-I at week 6
Kane, 2003 Nasrallah, 2004 United States	PANSS total score Secondary measures: PANSS positive and negative factor scores, CGI scale.	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 Rispderidone 25 mg vs placebo, p<0.05 fopr 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
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), benzotropine (for EPS) , and beta-andrenoceptor antagonists (for akathisia) were allowed as required but were not administered prophylactically.
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.

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

Author, year Country Trial name	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Keck, 1998 United States	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	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
Kramer, 2007 United States, Romania, Turkey, Latvia, Lithuania, and India	Mean age = 41 years 51% men, Ethnicity 85% white	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

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

Author, year Country Trial name	Outcome scales	Method of outcome assessment and timing of assessment
Keck, 1998 United States	BPRS total score BPRS core item score CGI-S SANS total score BPRS depression cluster BPRS anergia factor score	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	PANSS CGI-S	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: Benzotropine: 7% vs 19% vs 8% Lorazepam: 82% vs 85% vs 90% Beta-andrenoceptor 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
Lindenmayer, 2005 (see Kane, 2003)	439	Multicenter, DB, randomized, PCT	see Kane 2003
Luthringer, 2007 Europe (Poland, France, and Romania)	42	RCT DB	Men and women (ages 18–45 years), with schizophrenia and schizophreniarelated 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
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.
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
Luthringer, 2007 Europe (Poland, France, and Romania)	9 mg paliperidone ER or matching placebo 14 days	7 day washout- 3 day baseline period	Yes

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

Author, year Country Trial name	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Lauriello, 2005 United States subanalysis of inpatients from Kane 2003	Mean age = 38 years Gender: 70% male Ethnicity: 42.6% Caucasian; 41.5% black; 24.5% Hispanic; 4.7% other	Schizophrenia: 91.1% Schizoaffective disorder: 8.8% Prior treatment with antipsychotic: 67.4%	NR/ NR/ 214 inpatients	140/ NR/ 74 inpatients
Lindenmayer, 2005 (see Kane, 2003)	Mean age 38 (SD 10) 75% male 42% African American, 42% white, 11% Hispanic, 6% other ethnicity	See Kane 2003	NR/NR/429	NR/ NR/ 429
Luthringer, 2007 Europe (Poland, France, and Romania)	Mean age 32.2 years (range 20-46) Gender- 67% male Ethnicity 97% white	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

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

Author, year Country Trial name	Outcome scales	Method of outcome assessment and timing of assessment
Lauriello, 2005 United States subanalysis of inpatients from Kane 2003	see Kane 2003	PANSS every 2 weeks, CGI every week.
Lindenmayer, 2005 (see Kane, 2003)	Patient VAS and investigator evaluation	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.
Luthringer, 2007 Europe (Poland, France, and Romania)	leep 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	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
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
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
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
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)
Lindenmayer, 2005 (see Kane, 2003)	See Kane 2003
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
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%
Lindenmayer, 2005 (see Kane, 2003)	See primary results for injection site pain	52% withdrew
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), Hyperglycaemia 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, Dysmenorrhoea 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
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

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

Author, year Country Trial name	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Marder, 2007 USA Funding Johnson & Johnson	Mean age 41.6 years 74% male	63% at least markedly ill on CGI-S	444/444/432	252/28/432

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

Author, year Country Trial name	Outcome scales	Method of outcome assessment and timing of assessment
Marder, 2007 USA Funding Johnson & Johnson	PANSS; CGI-S, Marder, PSP	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 Baselinea 8.0 (21.5) vs. 15.7 (18.9) vs. 17.5 (19.8) vs. 18.4 (19.9) Difference in LS Means 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	Placebo vs Paliperidone vs. Olanzapine n (%)	Total withdrawals 252 (57%)
USA	Total Number of Patients with Adverse Events 82 (77) vs. 171 (76) vs. 79 (72)	Due to Aes 8 (2%)
Funding Johnson & Johnson	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)	

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.
Peuskenns, 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
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 lorazapem
Peuskenns, 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

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

Author, year Country Trial name	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
McEvoy, 2007 USA	Mean age: 40.4 years 78% male Ethnicity NR	Mean body weight 83.8 kg Mean (SE) age at time of first hospitalization for schizophrenia 24 years	508/420/420	278/10 /410
Peuskenns, 2007 Bulgaria, India, Poland, Russia, and Ukraine	Mean age: 35 years 60% male Ethnicity NR	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

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

Author, year Country Trial name	Outcome scales	Method of outcome assessment and timing of assessment
McEvoy, 2007 USA	PANSS (Totalscore, 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.	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.
Peuskenns, 2007 Bulgaria, India, Poland, Russia, and Ukraine	PANSS score, Clinical Global Impression-Improvement (CGI-I)	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 scorea 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.
Peuskenns, 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.
Peuskenns, 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
Peuskenns, 2007 Bulgaria, India, Poland, Russia, and Ukraine	Stabilization phase Somnolence 19.3% Dizziness 6.4% Randomisation 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
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.
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.

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

Author, year Country Trial name	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed
Pigott, 2003 International	Mean age: 42.0 years 56.1% male 90.6% white 6.5% black 0.6% Asian/Pacific Islander 2.3% Hispanic/Latino	Mean baseline PANSS total score: 81.8	NR/ NR/ 310	194/ 2/ 297
Small, 1997 United States and Europe	Mean age: 22.3 years Gender: 71.2% male Ethnicity: 70.7% white; 19.3% black; 10% others	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

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

Author, year Country Trial name	Outcome scales	Method of outcome assessment and timing of assessment
Pigott, 2003 International	CGI-I CGI-S PANSS PANSS-BPRS	**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	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)	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 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Controlled studies					
Advokat, 2004 United States	Hospital charts and medical records from the Eastern Louisiana Mental Health System	Retrospective	September 1996 through September 2001	NR	Olanzapine: 20.6mg/day Risperidone: 5.3mg/day Quetiapine: 320.6mg/day Clozapine: 375mg/day
Advokat, 2003	Eastern Louisiana Mental Health System	Retrospective	1995-2001	5 years	olanzapine 332 days risperidone 376 days quetiapine 558 days clozapine 583 days
Agelink, 2001 Germany	Evangelical Hospital Gelsenkirchen, Germany	Retrospective	Mean: 14.1 days	NR	amisulpride: 400 mg/day, olanzapine: 20 mg/day, sertindole: 12 mg/day, clozapine: 100 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
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, Paraoid Schizophrenia, or Schizophrenia Undifferentiated	Mean age=40.6 years 31% male 50% africa american	398/100/100	NR/NR/100
Agelink, 2001 Germany	Medication-free inpatients with schizophrenia	Mean age: 33.7 years 68.8% Male Ethnicity NR	NR/NR/51	0/0/51

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	Maxiumum daily dosages 28 of 46 patients on olzanzipine 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: olanzapin (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 risperidons = 1.67 vs 1.47 months
Agelink, 2001 Germany	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
Controlled studies	
Advokat, 2004 United States	NR
Advokat, 2003	NR
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Controlled studies	
Advokat, 2004 United States	
Advokat, 2003	
Agelink, 2001 Germany	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Al-Zakwani, 2003 United States	Multicenter, United States	Retrospective	24 months	18 months	Doses not reported. Interventions-Typical Antipsychotics: chlorpromazine, haloperidol, thioridazine, perphenazine, other; Atypical Antipsychotics: risperidone, olanzapine, quetiapine, clozapine
Ascher-Svanum, 2004 Faries, 2005 USA	U.S. Schizophrenia Care and Assessment Program (US SCAP)	Prospective	July 1997 to 2003	One year	Olanzapine Risperidone
Barak, 2004 Israel	Abarbamel Mental Health Center, Bat-Yam	Retrospective	January 1998 to December 2002	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
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/developmenal delays, mental retardation/Alzheimer's/Parkinson's diseases	Mean age: 38.5 years 59% Male Ethnicity NR	2710/833/469	NR/NR/469
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
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
Al-Zakwani, 2003 United States	Typical Antipsychotics: # dose adustments: 14(16.5%) # treatment augmenation: 1(1.2%) # requiring treatment switch: 11(12.9%) # receiving mixed therapy: 1(1.2%) Atypical Antipsychotics: # dose adustments: 128(30.4%) # treatment augmenation: 3(0.8%) # requiring treatment switch: 70(18.2%) # receiving mixed therapy: 7(1.5%)
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. <u>Odds of staying on monotherapy during the 1-year period (versus initiating polytherapy) (Faries 2005)</u> Olanzapine versus quetiapine: OR 2.08 (95% CI 1.30, 3.31) Olanzapine versus risperidone: OR 1.36 (95% 1.01, 1.84)
Barak, 2004 Israel	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
Al-Zakwani, 2003 United States	NR
Ascher-Svanum, 2004 Faries, 2005 USA	NR
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	Comments
Al-Zakwani, 2003 United States	
Ascher-Svanum, 2004 Faries, 2005 USA	
Barak, 2004 Israel	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Barner, 2004 United States	Database: Cenral 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	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	same as Dossenbach 2004	same as Dossenbach 2004	same as Dossenbach 2004
Bond, 2004 United States	A psychiatric rehabilitation agencym and four community mental health centers.	Prospective	March 1999 to January 2001	9 months	Olanzapine 12.9 mg Risperidone 5.4 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
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

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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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)
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Barner, 2004 United States	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	
Bond, 2004 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Brown, 2005 United States	Review of charts of VA patients	Retrospective	June 2001 to March 2003	NR	Ziprasidone Olanzapine
Buse, 2003 United States	AdvancePCS Inc	Retrospective	≥2 years	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	Database: Regie de l'Assurance Maladie du Quebec	Retrospective	1/1/97 to 12/31/99	NR	Olanzapine Risperidone
Conley, 1999 United States	Record review: Maryland state psychiatric facilities	Prospective	3/14/94 to 12/31/95	NR	Clozapine Risperidone
Cooper, 2005 Canada	Database: Quebec health insurance database and Quebec database for hospitalizations	Retrospective	July 1, 1996 through August 31, 2006	1 year	Olazapine 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
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
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
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
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
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
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 intitial 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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
Brown, 2005 United States	NR
Buse, 2003 United States	Hazard ratio of developing diabetes comparing antipsychtoics 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)
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Brown, 2005 United States	
Buse, 2003 United States	
Caro, 2002 Quebec	
Conley, 1999 United States	
Cooper, 2005 Canada	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Cooper, 2007 Canada	Database: Quebec health insurance board and Quebect registry of hospitalizations	Retrospective	January 1, 1997 to August 31, 1999	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 Hight intensity Olanzapine= >10mg/day; Risperidone= >4mg/day; Clozapine= >425mg/day; Quetiapine= >300mg/day
Coulter, 2001 International	Database: Uppsala Monitoring Centre in Sweden	Unclear	NR	NR	Clozapine Olanzapine Quetiapine Risperidone
de Haan, 1999 Netherlands	University of Armsterdam	Retrospective	7.3 months average	NR	clozapine: NR other drugs: NR
de Haan, 2002 Netherlands	Academic Medical Center, University of Amsterdam	Prospective	6 weeks	NR	Olanzapine(N=39): 14.2mg Risperidone(N=23): 4.1mg
de Leon, 2004 United States	Clinical Research Center, Norristown State Hospital, Norristown	Retrospective	16 weeks	NR	All patients switched from 4 weeks on 10 mg/day of haloperidol, to 100, 300, 600 mg/day clozapine
Dinakar, 2002 United States	Rockland Psychiatric Center, NY	Retrospective	3 months	NR	at Endpoint: olanzapine: 52.75 risperidone: 52.53

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
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
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
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
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
Cooper, 2007 Canada	NR
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Cooper, 2007 Canada	
Coulter, 2001 International	
de Haan, 1999 Netherlands	
de Haan, 2002 Netherlands	
de Leon, 2004 United States	
Dinakar, 2002 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Dolder, 2002 United States	Database: VA San Diego Healthcare System	Retrospective	NR	12 months	Haloperidol 8mg/day Perphenazine 12mg/day Risperidone 4mg/day Olanzapine 12.5mg/day Quetiapine 400mg/day
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 - NR planned exposure 3 yrs)		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
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
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
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.
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
Dolder, 2002 United States	NR
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)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Dolder, 2002 United States	
Dossenbach et al, 2004 27 countries in Africa, Asia, Europe, Central and South America and the Middle East IC-SOHO Study (6 month data)	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	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)	Same as Dossenbach 2004	same as Dossenbach 2004	12 months	NR	Same as Dossenbach 2004
Etminan, 2003 Ontario	Database: Ontario Drug Benefit (ODB) claims database	Unclear	NR	NR	Olanzapine Quetiapine Risperidone
Feldman, 2004 United States	AdvancePCS Inc	Retrospective	6-9 months	NR	NR
Fuller, 2003 Ohio	Database: Veteran's Integrated Service Network 10	Retrospective	1/1/97 to 12/31/00	NR	Risperidone 2.8 mg Olanzapine 10.0 mg Fluphenazine 12.2 mg Haloperidol 8.4 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
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)
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

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)
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety 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)	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 <u>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</u> 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)
Etminan, 2003 Ontario	Diabetes Diabetic events (% patients): Olanzapine=2.1 Quetiapine=1.0 risperidone 2.1
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	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)	
Etminan, 2003 Ontario	Age - older adults
Feldman, 2004 United States	
Fuller, 2003 Ohio	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Ganguli, 2001 United States	Multiple sources	Retrospective	4 months	NR	NR
Garcia-Cabeza, 2003 Montes, 2003 Spain Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	Multicenter Controlled	see above	see above	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)	Prospectively collected, multicenter study data	Prospective	6 mo (interim analysis of planned 3-yr term)	NR	Olanzapine 11.1 mg/day (SD 5.0) Risperidone 4.6 mg/day (SD 2.6)
Gianfrancesco, 2006a United States	Database: PharMetrics	Retrospective	January 1999 through August 2003	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
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
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 reponse 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)	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
Ganguli, 2001 United States	NR
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)	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	<u>Comparisons of treatment duration</u> 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
Ganguli, 2001 United States	Change in Mean Body Weight/BMI at Endpoint: Weight: risperidone: 82.8kg, P=NS olanzapine: BMI: risperidone: olanzapine:
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)	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	Comments
Ganguli, 2001 United States	
Garcia-Cabeza, 2003 Montes, 2003 Spain	Subjective Response Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)
Gasquet, 2005 Europe (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK)	
Gianfrancesco, 2006a United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Gianfrancesco, 2006b United States	Medical and prescription claims data for commercially insured patients	Retrospective	1999 to August 2003	Unclear	Risperidone, olanzapine, quetiapine, ziprasidone mean dosages NR
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	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	Database: Blue Cross/Blue Shield claims database	Retrospective	April 1997 through October 2000	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
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	Comments
Gianfrancesco, 2006b United States	
Gianfrancesco, 2002 United States	
Gianfrancesco, 2003a United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
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	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	Database: Michigan Medicaid administrative claims data set from Michigan's Department of Community Health (MDCH)	Retrospective	January 1996 through September 1997	1 year	Mean initial dosages: olanzapine 9.9mg risperidone 3.8mg haloperidol 18.2mg
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	Olanzapine 13.01 mg Risperidone 5.39 mg Haloperidol 13.64 mg	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, 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 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
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

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 haloperidole
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Gianfrancesco, 2003b United States	
Gibson, 2004 United States	
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Gupta, 2004 United States	Olean General Hospital at the SUNY Upstate Medical University at Syracuse	Prospective	NR	10 weeks	Quetiapine 4 weeks 392.5 mg/day
Haro, 2006 SOHO (secondary publication) 3-year effectiveness Europe	Same as Haro 2005	Same as Haro 2005	NR	3 years	Same as Haro 2005
Haro, 2006 SOHO (secondary publication) 12-month medication maintenance outcomes Europe	Same as Haro 2005	Same as Haro 2005	NR	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
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
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
Gupta, 2004 United States	Positive and Negative Syndrome Scale (PANSS): NS Simpson-Angus-Scale (SAS): NS
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
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
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) * $p \leq 0.05$.
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	Comments
Gupta, 2004 United States	Patients switched from olanzapine to quetiapine
Haro, 2006 SOHO (secondary publication) 3-year effectiveness Europe	
Haro, 2006 SOHO (secondary publication) 12-month medication maintenance outcomes Europe	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Haro, 2006 SOHO (secondary publication) 3-year remission/relapse outcomes Europe	Same as Haro 2005	Same as Haro 2005	NR	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
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	Comments
Haro, 2006 SOHO (secondary publication) 3-year remission/relapse outcomes Europe	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Haro, 2005 Europe SOHO (primary publication)	Prospectively collected, multicenter study data	Prospective	6 mo (interim analysis of planned 3-yr term)	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)
Hayhurst, 2002 UK	South Manchester University Hospitals NHS Trust	Retrospective cohort Controlled	NR	2 years	Clozapine 425 mg/day other antipsychotics: not specified
Hedenmalm, 2002 International	WHO database	Retrospective	Median treatment duration: R: 13 days, C: 52 days, O: 115 days	NR	Risperidone Clozapine 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
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)
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

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
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
Haro, 2005 Europe SOHO (primary publication)	NR
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Haro, 2005 Europe SOHO (primary publication)	Only data abstracted for olanzapine, risperidone, quetiapine, clozapine arms
Hayhurst, 2002 UK	
Hedenmalm, 2002 International	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Hennessy, 2002 United States	3 US Medicaid programmes	Retrospective	NR	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
Ho, 1999 United States	Mental Health Clinical Research Center, University of Iowa	Retrospective	4 weeks	6 months	Risperidone 6.0 mg/day (N=21) Olanzapine 13.7 mg/day (N=21)

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
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
Ho, 1999 United States	Schizophrenia	Mean age: 31.5 years 76.2% male Ethnicity NR	NR/NR/42	NR/NR/26

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Hennessy, 2002 United States	Adjusted rate ratios; 95% Cis Patients with glaucoma: cardiac arrest/ventricular arhythmia; 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 arhythmia; 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)
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)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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
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)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Hennessy, 2002 United States	
Ho, 1999 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Hodgson, 2005 England	Case Notes: 26 consultant psychiatrists	Retrospective	1994 to 2001	NR	Clozapine=332.3mg/day Olanzapine=12.1mg/day Risperidone=4.7mg/day
Jerrell, 2007 United States	Medical and pharmacy claims information	Retrospective	July 1, 2002 to June 30, 2004	NR	Atypical antipsychotics: Aripiprazole Ziprasidone Quetiapine Risperidone Olanzapine Clozapine Typical antipsychotics: Haloperidol Fluphenazine
Joyce, 2005 United States	Medical and pharmaceutical claims from the PharMetrics Patient-Centric Database	Retrospective	March 1, 2001 and August 31, 2003	≥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	Prospective	≥ 1 year	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
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
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
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
Jerrell, 2007 United States	Health Outcomes For cerebrovascular conditions, there were no significant differences between groups For heart disease conditions, aripipracole 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 significanly 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 postindex periods was not significantly different among the treatment groups. Psychiatric-related costs decreased significanly 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
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.
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	Comments
Hodgson, 2005 England	
Jerrell, 2007 United States	
Joyce, 2005 United States	
Kane, 1993 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Kasper, 2001 9 countries in Europe and Australasia	Riverview Hospital , British Columbia	Retrospective	4 months	NR	Risperidone (N=30) : 4.89 mg/day vs. olanzapine (N=30): 17.19 mg/day
Koller, 2003 United States	Food and Drug Administration Med Watch	Retrospective	9 years	NR	Risperidone, haloperidol
Koro, 2002 UK	England and Wales-based General Practice Database, Bristol-Myers Squibb, MEDTAP	Retrospective	30 months	NR	Olanzapine: dose range NR Risperidone: dose range NR Conventional antipsychotics
Koro, 2002b UK	United Kingdom based General Practice Research Database	Retrospective	NR	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
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
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 presciptions 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
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
Koller, 2003 United States	Risperidone-associated hyperglycemia: N=131 Combined risperidone-haolperidol associated hyperglycemia: N=7 Haloperidol-associated hyperglycemia: N=13 Reports of acidosis with absesnce 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
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
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 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	Comments
Kasper, 2001 9 countries in Europe and Australasia	
Koller, 2003 United States	
Koro, 2002 UK	
Koro, 2002b UK	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Kraus, 1999 Germany	Max Planck Insitute of Psychiatry	Retrospective	4 weeks	1 week	Clozapine: 170 mg/day Olanzapine: 13 mg/day Haloperidol: 5 mg/day
Kurz, 1995 Austria	Single center Active control	First-time clozapine users	Mean weeks: clozapine=23.2, haloperidol=5.2 23.2 weeks	Clozapine 193.7 mg Haloperidol 12.8 mg	Anticholinergics Beta blockers
Lambert, 2005 Australia	Medical record review	Retrospective	1998 to 2000	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; pvalue 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
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	Comments
Kraus, 1999 Germany	
Kurz, 1995 Austria	
Lambert, 2005 Australia	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	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)	Same as Haro 2005	Same as Haro 2005	Initial recruitment period of 9/1/00-12/31/01	6 months	Same as Haro 2005
Lambert, 2006 United States	Veterans Health Administration of the Department of Veterans Affairs (VA)	Retrospective	October 1, 1996 to September 30, 2001	NR	Olanzapine Risperidone Quetiapine Haloperidol
Lambert, 2005 United States	California Medicaid	Retrospective	July 1, 1997 to December 31, 2000	NA	More than 12 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
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
Lambert, 2005 United States	Schizophrenia	NR	129341/34337/12637	NR/NR/12637

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).
Lambert, 2005 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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
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)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Lambert, 2005 SOHO (secondary publication) 6-month tolerability results Europe (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain, and the UK)	
Lambert, 2006 United States	
Lambert, 2005 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
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	12 months	Same as Dossenbach 2004
Lee, 2002 United States	Database: Protocare Sciences's 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	Patients were observed 365 days after their index dates.	Clozapine Olanzapine Quetiapine Risperidone Typical APs Mean doses NR
Leon, 1979	Hospital Psiquiatrico, Columbia	Retrospective	6 weeks	3-4 years	NR
Leslie, 2004 United States	Department of Veteran Affairs	Retrospective	3 months	NR	Clozapine, olanzapine, quetiapine, risperidone: 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
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
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 diagnsis 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	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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
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 opint 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)
Lee, 2002 United States	NR
Leon, 1979	Mean number of required re-hospitalizations: clozapine: 1.89 vs chlopromazine: 3.52; P<0.01 Average time spent spent in hospital: clozapine: 44.8 days vs chlopromazine: 272.8 days; P<0.05 Average mean time for re-admission: clozapine: 260 days vs chlopromazine: 229
Leslie, 2004 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
Lee, 2006 IC-SOHO sub-study in Asian country participants 12-month outcomes Korea, Taiwan and Malaysia	Tardive dyskinesia % 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) Weight increase of ≥ 7% % patients: olanzapine=51.4% risperidone=29.8% typicals=20.5% OR (95% CI) risperidone vs olanzapine=0.38 (0.21, 0.68) typicals vs olanzpaine=0.27 (0.12, 0.64) typicals vs risperidone=0.72 (0.29, 1.81)
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	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%

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Lee, 2006 IC-SOHO sub-study in Asian country participants 12-month outcomes Korea, Taiwan and Malaysia	
Lee, 2002 United States	
Leon, 1979	
Leslie, 2004 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Lin, 2006 Taiwan	Chart reviews	Retrospective	7/1/01-6/30/02	2 years	Clozapine, risperidone, typical antipsychotics
Lucey, 2003 Ireland	Irish Risperidone Olanzapine Drug Outcomes in Schizophrenia	Retrospective	Mean duration: 37.8-40.5 days	NR	risperidone: 4.2 mg/day olanzapine: 12.9 mg/day
Madhusoodanan, 1999 United States	St. John's Episcopal Hospital	Retrospective	4 months	NR	Mean daily doses: risperidone(N=114): 3mg olanzapine(N=37): 10mg
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	Olanzapine=333 Quetiapine=324 Risperidone=280 (days)	Olanzapine 14.7 mg Quetiapine=324mg Risperidone=3.5 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
Lin, 2006 Taiwan	Schizophrenia	82% male Mean age=39.2 years 100% Taiwanese	NR/NR/382	83 (22%)/NR/382
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 Ethncity NR	NR/NR/151	22%/NR/151
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
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
Lucey, 2003 Ireland	Hospitali Stay: % discharged on or before day 120: R 95% vs O 94% (NS) Mean legth 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%
McIntyre, 2003 Williams, 2006 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Admission to hospital for any reason: n/N (%) 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%)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
Lin, 2006 Taiwan	NR
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
McIntyre, 2003 Williams, 2006 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	Mean weight gain (kg) Olanzapine=3.72 Quetiapine=7.55 Risperidone=1.62 ≥ 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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Lin, 2006 Taiwan	
Lucey, 2003 Ireland	
Madhusoodanan, 1999 United States	
McIntyre, 2003 Williams, 2006 Canada Canadian National Outcomes Measurement Study in Schizophrenia (CNOMSS)	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Meyer, 2002 United States	Oregon State Hospital	Retrospective	July and August 1999	1 year	risperidone (N=47): 4.5 mg/day olanzapine (N=47): 16.7 mg/day
Miller, 1998 United States	Innsbruck University Clinics, Austria	Retrospective	≥3 months	NR	clozapine: 425.6 mg/day risperidone: 4.7 mg/day conventional antipsychotics: 476.5 mg/day
Modai, 2000 Israel	Database: Sha'as Menashe Mental Health Center (Israel)	Unclear	1/91 to 8/97	NR	Clozapine Other psychiatric agents (non-clozapine treated)
Moisan, 2005 Canada	Database from the Prescription Drug Insurance Plan administered by the Quebec Health Insurance Board	Retrospective	January 1, 1997-August 31, 1999	NR	Olanzapine Risperidone
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	Olanzapine 13.5 mg Risperidone 5.4 mg Haloperidol 12.4 mg	High potency antipsychotics Low potency antipsychotics Benzodiazepines Anticholinergics Antidepressants Mood stabilizers

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
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
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)
Moisan, 2005 Canada	All drug beneficiaries who had received at least one prescription of an atypicl 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
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
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
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
Moisan, 2005 Canada	Those taking olanzapine were more likely to need to be started on a diabetic and/or lipids meidcation than those taking risperidone
Montes, 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
Meyer, 2002 United States	Triglycerides: O: + 104.8 mg/dL vs R: +31.7 mg/dL (P=.037) Cholestrol: 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)
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
Moisan, 2005 Canada	NR
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Meyer, 2002 United States	
Miller, 1998 United States	
Modai, 2000 Israel	
Moisan, 2005 Canada	
Montes, 2003 Spain Sub-group Analysis from Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapine (EFESO)	First Episodes

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Novick, 2005 SOHO (secondary publication) Europe	Prospectively collected, multicenter study data	Prospective	6 mo (interim analysis of planned 3-yr term)	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)
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	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	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	NR	Haloperidol Risperidone 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
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)
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 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	Schiophrenia, schizoaffective disorder	Mean age: NR Gender: NR 45% White 39% African American	NR/NR/3583	NR/NR/3583

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Novick, 2005 SOHO (secondary publication) Europe	NR
Ollendorf, 2004 United States	NR
Opolka, 2003 United States	<u>Adherence to index antipsychotic</u> 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) Mexian 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)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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%)
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.
Opolka, 2003 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Novick, 2005 SOHO (secondary publication) Europe	
Ollendorf, 2004 United States	This analysis controlled for total duration of therapy and number of prescriptions. Actual mean doses are not reported.
Opolka, 2003 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Ostbye, 2004 United States	Database: AdvancePCS records on prescription drugs dispensed to beneficiaries (n=170030 from 50 states)	Retrospective	2000-2002	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
Peacock, 1996 Denmark	Naturalistic: St. Hans Hospital; Copenhagen's Municipal Psychiatric Hospitals in Glostrup and Ballerup	Prospective	1 year	NR	Clozapine CAPD
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	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
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
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
Ostbye, 2004 United States	NR
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
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)
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	Comments
Ostbye, 2004 United States	Exposure classification is binary (did or did not receive prescription for each drug or class); dose and duration of treatment are not controlled for
Peacock, 1996 Denmark	
Pelagotti, 2004 Italy	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Philippe, 2005 France	Principal public psychiatric care units in France	Prospective	1993 to 2002	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
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
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
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	Comments
Philippe, 2005 France	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Procyshyn, 1998 Canada	Chart review from Riverview Hospital in British Columbia	Retrospective	6 weeks	NR	Mean Doses: risperidone: 5.3mg/day vs olanzapine: 14.5mg/day
Rascati, 2003 United States	Database: Texas Department of Health Medicaid Program	Retrospective	January 1996 through August 1999	1 year	olanzapine: 12.87mg/day risperidone 4.40mg/day
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)	NR	Oral or depot conventional antipsychotic Clozapine 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
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
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

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% <u>Affects on medication choice:</u> 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 ilnness as a comorobid 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% <u>Schizophrenia related costs:</u> 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 <u>Total health care costs:</u> Previous hospitalization or history of clozapine use was associated with an increase of $3424 (US) per year and $2451 (US) per year, respectively
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 docotor visits compared to those taking either form of conventional antipsychotic, while risperidone takers had a higher number of docotor 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.

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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
Remington, 2001 Canada	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Procyshyn, 1998 Canada	
Rascati, 2003 United States	
Remington, 2001 Canada	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
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	1 year	Olazapine Risperidone
Rettenbacher, 2006 Austria	Laboratory measurements of included subjects	Prospective	NR	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
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	Schiophrenia	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
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 olanzipine initiators Incidence of concomitant medications Those initiated on olanzipine 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 olanzipine 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
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	Comments
Ren, 2006 United States	
Rettenbacher, 2006 Austria	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Ritsner, 2006 Ritsner, 2004 Israel	Sha'ar Menashe Mental Health Center Case Register	Prospective	NR	1 year	Olanzapine 15.2 mg/day Risperidone 4.4mg/day Typical antipsychotics mean dose NR
Sax, 1998 United States	University of Cincinnati Medical Center site	Prospective	NR	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
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	Comments
Ritsner, 2006 Ritsner, 2004 Israel	
Sax, 1998 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Schillevoort, 2001 Netherlands	PHARMO-database	Retrospective	90 days	NR	haloperidol: 2.2 mg/d, risperidone: 54 mg/d, olanzapine mg/d
Schillevoort, 2001b Netherlands	PHARMO-database	Retrospective	90 days	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 chlopromazine: 63 mg/day
Sernyak, 2002 United States	Veterans Health Administration of the Department of Veterans Affairs (VA)	Retrospective	October 1, 1999 to September 30 1999	4 months	Clozapine, olanzapine, risperidone, quetiapine
Sharif, 2000 United States	Creedmoor Psychiatric Center, Columbia University	Retrospective	12 weeks	4 weeks	Clozapine: 520 mg/day Risperidone: 7.5 mg/day
Snaterse, 2000 Canada	Alberta Hospital Edmonton	Retrospective	12 months	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
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
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
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 thioidazine: 3.12 (1.21, 8.04) risperidone vs pipamperone: 4.25 (1.54, 11.72) risperidone vs chlopromazine: 2.97 (0.35, 24.97)
Sernyak, 2002 United States	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	Comments
Schillevoort, 2001 Netherlands	
Schillevoort, 2001b Netherlands	
Sernyak, 2002 United States	
Sharif, 2000 United States	
Snaterse, 2000 Canada	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Soholm, 2003 Denmark	Patient records from the Psychiatric University Clinic, Rigshospitalet, Copenhagen University Hospital, Denmark	Retrospective	>1997	NR	1st line of treatment: conventional antipsychotic or clozapine 2nd line of treatment: atypical antipsychotic
Soyka, 2005 Germany (inpatients)	Psychiatric Hospital of the University of Munich Non-randomized, comparative	Prospective	Current hospitalization time (weeks), risperidone vs hal: 6.8 vs 6.2 weeks	NR	Average dose /d Risperidone: 4.6 mg/d Halperidol: 10.4 mg/d
Spivak, 1998 Israel	Naturalistic: Ness-Ziona Mental Health Center	Prospective	1 year	NR	Clozapine 295 mg CAPD (chlorpromazine equivalent) 348.9 mg
Strassnig, 2007 United States	Subset of data from larger ongoing trial	Unclear	1990-2006	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 significanly fewer days in the hospital (P=0.001)
Soyka, 2005 Germany (inpatients)	Driving ability tests (all subjects had licences), risperidone vs halperidol 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 halperidol vs control: PVT (peripheral vision test with tracking task, incl. reaction time): 5 vs 13 vs 0 TT15 (tachistoscope test, abililty 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 significanly more weight gain during the 1-year observation period and their body mass index increased to a significanly 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
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
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	Comments
Soholm, 2003 Denmark	
Soyka, 2005 Germany (inpatients)	Tests are relevant to the German Road Traffic Safety Board.
Spivak, 1998 Israel	
Strassnig, 2007 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Strous, 2006 Israel	Clinic visits	Prospective	NR	12 weeks	Risperidone, olanzapine, clozapine
Su, 2005 Taiwan	Clinic visits	Prospective	NR	3 months	Olanzapine 7.9mg, risperidone 2.5mg
Swanson, 2004 United States	Medical records from the North Carolina site of the Schizophrenia Care and Assessment Program	Retrospective	1997 to 1999	3 years	Olanzapine Risperidone
Taylor, 2006 UK- Scotland	Not reported	Prospective	2002 plus 6 month follow-up	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, 2003 UK	U.K. Risperidone Olanzapine Drug Outcomes Studies in Schizophrenia program (RODOS-UK)	Retrospective	4 months	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
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, 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, 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
Swanson, 2004 United States	Olanzapine takers had a reduced probability of vioelnce 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, 2006 UK- Scotland	Mean change from baseline and % change CGI Amisulpride 0.85 19% Clozapine 1.80 34% Olanzapine 1.18 33% Quetiapin 0.83 11% Positive symps Amisulpride 0.55 30% Clozapine1.50 54% Olanzapine 0.9 51% Quetiapin 0.67 26% Negative symps Amisulpride 0.40 24% Clozapine 0.40 20% Olanzapine 0.26 11% Quetiapin 1.00 39% Side effects, Amisulpride 0.87 54% (1.5) Clozapine 0.10 13% Olanzapine 0.90 51% Quetiapin 1.50 53% Qualityof life, Amisulpride 0.38 15% Clozapine 1.10 34% (1.7)Olanzapine 0.96 36% Quetiapin 1.17 31%
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
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
Swanson, 2004 United States	NR
Taylor, 2006 UK- Scotland	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	Comments
Strous, 2006 Israel	
Su, 2005 Taiwan	
Swanson, 2004 United States	
Taylor, 2006 UK- Scotland	
Taylor, 2003 UK	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Tiihonen, 2006 Finland	Community care	Prospective	1996-2001	3.6 years	Olanzapine, clozapine, risperidone, oral perphenazine, thioridazine, perphenazine depot, chlorprothixene, chlorpromazine, haloperidol, and levomepromazine
Verma, 2001 United States	Houston VA Medical Center	Retrospective	Average: 25 days	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
Tiihonen, 2006 Finland	All people in Finland who were hospitalised 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 hospitalised in Finland	0/0/2230
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
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 hospitalisation, 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)
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
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)
Verma, 2001 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Tiihonen, 2006 Finland	
Verma, 2001 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Voruganti, 2000 Voruganti, 2002 Canada	Western Ontario schizophrenia research program	Retrospective	NR	≥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, trifluperazine

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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Voruganti, 2000	85% of patients benefitted from switching from conventional to novel antipsychotics
Voruganti, 2002	8(6%) preferred conventional treatment
Canada	Remained on maintenance treatment: risperidone 82% olanzepine 86% quetiapine 82% CAPD (n=44) vs risperidone (n=50) vs olanzepine (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 antypsychotic drugs risperidone (n=43) vs olanzepine (n=44) vs quetiapine (n=31) Syptoms 1. PANSS: -23.63 vs -23.67 vs -21.43 a. positive symptoms cluster: -5.18 vs -4.11 vs -4.67 b. negative symtoms 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)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
Voruganti, 2000	CAPD (n=44) vs risperidone (n=50) vs olanzepine (n=48) vs quetiapine (n=42) vs clozapine (n=46)
Voruganti, 2002 Canada	Drug attitute 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 antypsychotic drugs risperidone (n=43) vs olanzepine (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)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Voruganti, 2000 Voruganti, 2002 Canada	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Wang, 2002 U.S.	Databases: NJ Medicaid program & NJ Pharmacetuical Assistance to the Aged & Disabled program plus Medicare	Retrospective	6 months before date of 1st prescription for insulin or oral hypoglycemic agent	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
Weiser, 2000 Israel	Tel-Aviv University Medical School	Retrospective	NR	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	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	NR	Clozapine, olanzapine, risperidone, quetiapine, haloperidol, fluphenazine/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
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
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Wang, 2002 U.S.	NR
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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)
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 cholestrol levels from baseline: risperidone: -6%, p=.04 fluphenazine: -6%; p=.04 13% of olanzapine patients (4) required increases in doses of lipid-loweing agents after beginning treatment

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Wang, 2002 U.S.	Duration of treatment and previous treatment with clozapine, prior to the 6-month window of observation were not included in the analysis.
Weiser, 2000 Israel	
Wirshing, 2002 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Zhao, 2002 United States	Database: IMS Health Life Link: Integrated Claims Solutions	Retrospective	October 1, 1996 through December 31, 1998	1 year	Olanzapine= 10.45mg/day Risperidone= 3.32mg/day
Zhao, 2002 United States	IMS Health Lifelink: Integrated Claims Solutions	Retrospective	Average: 181-217 days	NR	risperidone(N=985): 4.02 mg olanzapine(N=348): 10.49 mg
Uncontrolled studies					
Alvarez, 1997 Spain	Naturalistic: Psychiatry Dept of the Hospital de Sant Pau since 1984 (Spain)	Prospective	6.7 years (mean)	NR	Clozapine 266.9 mg (mean)
Atkin, 1996 UK/Ireland	Database: Clozaril Patient Monitoring System (CPMS)	Retrospective	1/7/90 to 7/3/94	NR	Clozapine 313 mg
Buckman, 1999 United States	Database: Illinois Dept of Mental Health and Developmental Disability	Unclear	1990 to 1995	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
Zhao, 2002 United States	Schizophrenia	Mean age: 48.6 years 53.5% male Ethnicity NR	NR/NR/1333	0/0/1333
Uncontrolled studies				
Alvarez, 1997 Spain	Treatment resistent 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 iniatiated 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 signficiantly less likely to be prescribed an anti-Parkisonian 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)
Zhao, 2002 United States	Average days of treatment: O: 217 vs R: 181; P<.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
Zhao, 2002 United States	NR
Zhao, 2002 United States	NR
Uncontrolled studies	
Alvarez, 1997 Spain	Weight increase (patients): 11 (13%) Seizures (patients): 3 (3%) Serious hematological side-effects: None
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	Comments
Zhao, 2002 United States	
Zhao, 2002 United States	
Uncontrolled studies	
Alvarez, 1997 Spain	Responders vs Nonresponders
Atkin, 1996 UK/Ireland	
Buckman, 1999 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Bunker, 1996 United States	Clozapine patient monitoring system	Prospective	February 1990 to January 1996	3 years	clozapine for 643 days
Conley, 1997 United States	Spring Grove Hospital Center	Prospective	1990-1995	12 months	clozapine 468 mg/day 12 months
Deliliers, 2000 Italy	Database: Italian Clozapine Monitoring System (ICLOS)	Unclear	1995 to 1999	NR	Clozapine 200-350 mg
Devinsky, 1991 United States	Chart review	Unclear	1972 to 1988	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
Bunker, 1996 United States	44.4% paranoid 31.1% undifferenctiated 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
Deliliers, 2000 Italy	Treatment resistant schizophrenia	Mean age NR 63% male Race NR	NR NR 2404	NR NR 2404
Devinsky, 1991 United States	Treatment-resistent schizophrenia	NR NR NR	1418 1418 1418	NR NR 1418

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 agergia: 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 factore: 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
Deliliers, 2000 Italy	NR
Devinsky, 1991 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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 compelete resolution of DE
Conley, 1997 United States	1 cardiovascular side effect
Deliliers, 2000 Italy	Agranulocytosis 16 cases (0.7%)
Devinsky, 1991 United States	Seizures # cases=41/1418 (2.9%)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Bunker, 1996 United States	
Conley, 1997 United States	
Deliliers, 2000 Italy	
Devinsky, 1991 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Dossenbach, 2000 Israel	5 study centers	Prospective	NR	18 weeks	olanzapine 5-25 mg/day 18 weeks
Drew, 2002 Australia	Database: Clozaril Patient Monitoring System (CPMS)	Retrospective	5 years	NR	Clozapine
Eberhard, 2006 Sweden	Multicenter	Prospective	NR	5 years	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
Dossenbach, 2000 Israel	chronic schizophrenia	NR	50/NR/48	5/3/48
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
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- achived some degree of improvement: 24(53.3%) Patient Globol Impression- improvement: 23(51%)
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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
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%
Eberhard, 2006 Sweden	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Dossenbach, 2000 Israel	
Drew, 2002 Australia	Clozapine-naïve; commenced Clozapine in Australian Capital Territory (ACT) before 7/1/94
Eberhard, 2006 Sweden	Multiple analyses with subgroups and subcomparisions by diagnosis. I had a hard tiime piecing out the different results and what groups were being compared.

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
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)	No follow-up (snapshot)	Clozapine Typical APs Mean dose NR
Henderson, 2005 United States	Autopsy reports, medical records	Retrospective	January 1992 to December 2003	90 months	Clozapine; dose NR
Henderson, 2000 United States	Chart review: outpatient clinic of urban mental health center	Retrospective	5 years	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
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, 2005 United States	Schizophrenia Schizoaffective disorder	Mean age=36.5 years 72% male 89% white	NR NR 96	N/A N/A 96
Henderson, 2000 United States	Schizophrenia Schizoaffective disorder	Mean age=36.35 73.2% male 91.5% white	NR 101 82	NR NR 82

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Hagg, 1998 Sweden	NR
Henderson, 2005 United States	NR
Henderson, 2000 United States	NR

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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)
Henderson, 2005 United States	Kaplan-Meier estimates for overall 10-year: Mortality=9% New-onset diabetes=34% <u>Subgroup analyses for odds of mortality (95% CI)</u> African American vs white: 7.2 (0.7, 69.9) Hispanic vs white: 11.3 (1.1, 118.1) Age: 1.0 (0.868, 1.124) <u>Subgroup analyses for odds of new-onset diabetes (95% CI)</u> African American vs white: 11.5 (3.59, 36.88) Hispanic vs white: 4.3 (1.19, 15.55) Age: 1.02 (0.97, 1.07)
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)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Hagg, 1998 Sweden	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, 2005 United States	
Henderson, 2000 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Herrman et al, 2004 Canada	Database: administrative health care databases in Ontario, Canada	Retrospective	April 1, 1997 through March 31, 2002	NR	Risperidone Olanzapine Typical antipsychotics
Hofer, 2003 Austria	inpatients unit of the Department of Psychiatry of Innsbruck University Clinics	Prospective	1989-1996	8 weeks	Clozapine 263.5 mg/day for at least 8 weeks
Honigfeld, 1996 United States	Database: Clozapine National Registry System	Unclear	2/1990 to 12/1994	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
Herrman et al, 2004 Canada	Patients over age 65 who were given at least 2 successive prescriptions and received enourgh 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
Hofer, 2003 Austria	Schizophrenia or schizphreniform 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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
Herrman et al, 2004 Canada	NR
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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)
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%)

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Herrman et al, 2004 Canada	
Hofer, 2003 Austria	
Honigfeld, 1996 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Kane, 1994 United States	the inpatients sevice at Hillside Hospital	Prospective	NR	52 weeks	Clozapine 599 mg/day 52 weeks
Killian, 1999 Australia	Adverse Drug Reactions Advisory Committee (ADRAC) of Australia	Unclear	Jan. 1993 to March 1999	NR	Clozapine range: 100-725 mg/d myocartditis 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
Koller, 2001 United States	MedWatch Drug Surveillance System	Retrospective	January 1990 to February 2001	NR	Clozapine 362 mg
Kopala, 2005 Canada	Nova Scotia Early Psychosis Program in Halifax	Prospective open-label dase ranging study	NA	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.

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
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
Koller, 2001 United States	clozapine-associated diabetes or hyperglycemia	Mean age=40 years Gender: NR Ethnicity: NR	NR/NR/384	NA/NA/384
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
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
Koller, 2001 United States	NR
Kopala, 2005 Canada	See safety outcomes

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
Kane, 1994 United States	NR
Killian, 1999 Australia	Caradiomyopathy: 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
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
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Kane, 1994 United States	
Killian, 1999 Australia	
Koller, 2001 United States	
Kopala, 2005 Canada	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Kozma, 2004 (poster) United States	Database: Medstat's Medicaid database	Retrospective	1999-2002	NR	Atypical antipsychotics overall Olanzapine Risperidone Quetiapine Haloperidol Benzodiazepines
Lasser, 2004 United States	NR	Prospective	NR	8 weeks	Olanzapine or risperidone for 8 weeks
Lasser, 2004 Europe and Canada	Europe and Canada multicenter trial	Prospective	12 months	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
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 United States	Schizophrenia or schizoaffective disorders	Mean age=49.9 years 60.8% male 63.6% white	NR/NR/552	NR/NR/375
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
Kozma, 2004 (poster) United States	NR
Lasser, 2004 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
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 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
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	Comments
Kozma, 2004 (poster) United States	
Lasser, 2004 United States	
Lasser, 2004 Europe and Canada	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Lieberman, 1992 Alvir 1993 United States	Database: Caremark Patient Monitoring System (CPMS) from 2/5/90 to 4/30/91	Unclear	>/= 3 weeks	NR	Clozapine mean maximum dose=451.9 mg
Lindstrom, 1989 Sweden	Hosptial records and interviews	Retrospective	July 1, 1974 to December 31, 1986	NR	Clozapine
Lund, 2001 United States	Database: Iowa Medicaid program claims/prescription database	Unclear	1990 to 1994	Clozapine=25.5 months Typical APs =24.5 months	Clozapine Typical Aps
Mladsi, 2004 United States	Three acute care inpatient mental health facilities	Retrospective	May 1, 1998 and June 30, 2000	Length of stay- less than 30 days	Risperidone 4.45 mg Olanzapine 14.04 mg Quetiapine 350.33 mg
Rastogi, 2000 UK	NR	Prospective	NR	6 months	clozapine 150-300 mg 6 months
Reid, 1998 United States	Database: Texas MH System	Unclear	1991 to 1996	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
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
Lund, 2001 United States	Schizophrenia	Mean age=41.9 59.2% male Race NR	NR 4770 3013	NR NR 3013 (clozapine=552, CAPD=2461)
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
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Effectiveness outcomes
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.
Lund, 2001 United States	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)
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

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Safety outcomes
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. Commone, 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.
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
Mladsi, 2004 United States	NR
Rastogi, 2000 UK	NR
Reid, 1998 United States	Suicide 1 case Annual rate=12.74 per 1000,000

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Lieberman, 1992 Alvir 1993 United States	
Lindstrom, 1989 Sweden	
Lund, 2001 United States	Age
Mladsi, 2004 United States	
Rastogi, 2000 UK	
Reid, 1998 United States	

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Data source	Prospective Retrospective Unclear	Sampling frame	Exposure period	Interventions mean dose
Still, 1996 United States	a 400-bed state psychiatric hospital	Prospective	April to August 1994	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.
Umbricht, 1994 United States	Chart review	Retrospective	12 months		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	Chart review of first 100 pts starting clozapine treatment (Dammasch State Hospital; Wilsonville, Oregon)	Unclear	May 1990 to December 1991	1 year follow-up (as well as review of 6 months priort 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
Still, 1996 United States	Schizophrenia or schizoaffective disorder	Mean age=41.2 years 60% male Ethnicity: NR	NR/NR/10	5/0/5
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
Still, 1996 United States	No subjects improved after being switchd to risperidone PANSS, LPCF increased from baseline, but no significant changes: patients who were switched from clozapine tended to wersen 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 cgabge at week 6 through week 12 (data NR) CGI scores: 2 no change; 3 minimally worse; 4 much worse; 1 very much worse
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
Still, 1996 United States	3 decreased concentration 3 impaired memory 4 irritability 3 akathisia, confusion Akathesia scale showed significant different worsening of symptoms
Umbricht, 1994 United States	60% with ≥ 10% weight gain
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 withprevious head trauma had seizure

Evidence Table 6. Observational studies of safety and adverse events in patients with schizophrenia

Author, year Country	Comments
Still, 1996 United States	Patients switched from clozapine to risperidone
Umbricht, 1994 United States	72% neuroleptic-treatment resistent
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 pt reported to have died of pnuemonia (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
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
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).

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 : olanzapin= 57%, risperidone=38%, quentiapine = 64%, and clozapine = 14%	No; ≥ 3 months	Poor	
Agelink, 2001	Yes	Yes	Fair	
Alvarez, 1997 Spain	NR	Yes	Fair	
Al-Zakwani, 2003	Yes	Yes	Fair	
Ascher-Svanum, 2004 US-SCAP Study Interim Results	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?
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
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
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

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
Atkin, 1996 UK/Ireland	NR	Yes	Fair	
Barak, 2004	No; only commented regarding similarities in gender, age, distribution of diagnoses	Unclear	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	
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

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?
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
Deliliers, 2000 Italy	Yes	NR	Yes	Yes	Yes
Devinsky, 1991 United States	Yes	NR	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
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	
Deliliers, 2000 Italy	NR	Unclear	Fair	
Devinsky, 1991 United States	Yes	Unclear	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?
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
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
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

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
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	
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)
Feldman, 2004 Buse, 2003	Yes	Yes	Fair	
Fuller, 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?
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)
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 Medicaide data	Unclear, don't know reliability of the database
Gomez, 2000 Spain Estudio Farmacoepidemiologico en esquizofrenia con Olanzapine (EFESO)	Yes	Yes	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
Ganguli, 2001	No	Yes (4 months)	Fair	
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	

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?
Hagg, 1998 Sweden	Yes	NR	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
Ho, 1999	Unclear	No	Yes	Yes for group in the Longitudinal Study of Recent-Onset Psychosis, No for others	unclear, blinding NR
Hodgson, 2005	Unclear: groups differed but did adjust	NA (retrospective study including persons with available data only)	Yes	Yes, from pharmacy records	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
Hagg, 1998 Sweden	No	N/A, cross-sectional study	Fair	
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	
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	
Hodgson, 2005	Yes	Unclear: study interval 1994-2001 but unclear if all three groups had same median observation period	Fair	retrospective, 3-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?
Honigfeld, 1996 United States	Yes	NR	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
Joyce, 2005	No, multiple exclusions applied depending on data most available.	None	Yes	Yes	Yes
Kane, 1993 United States	No	NR	Yes	Yes	Yes
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

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
Honigfeld, 1996 United States	NR	Yes	Fair	
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	
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	Yes	Poor	Between group differences in gender and diagnosis
Kasper, 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?
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
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
Lublin, 2003	Yes	None	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
Lublin, 2003	No	12 weeks	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?
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
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

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
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	
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	

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?
Modai, 2000 Israel	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
Naber, 2001	Method NR, unable to determine.	No (4% missing SWN data, 3% missing PANSS data)	Yes	Yes	Not blinded
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

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
Modai, 2000 Israel	Yes	Unclear	Fair	
Moisan, 2005	Yes	6 months	Good	
Montes, 2003 Spain Sub-group Analysis from EFESO	Yes	Yes	Fair	
Naber, 2001	Yes	Yes	Fair	
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	

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?
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
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
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.

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
Phillippe, 2005	Yes	Yes	Fair	
Procyshyn, 1998	No	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	
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.	

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?
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)
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

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
Schillevoort, 2001a	Yes	Yes	Fair	
Schillevoort, 2001b	Yes	Yes	Fair	
Sernyak, 2002	Yes	Not sure- 4-month period studied.	Fair	
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	

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?
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
Taylor, 2005	Unclear	Yes	Yes	Yes	No
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
Tilhonen, 2006	Yes	None	Yes	Yes	Yes
Umbricht, 1994 United States	No	NR	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

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
Swanson, 2004	Yes	Yes (3 years)	Fair	Prospective, 2-group cohort
Taylor, 2005	No	No - 6 months	Poor	
Taylor, 2003	Yes	Yes	Fair	
Tilhonen, 2006	Yes	Yes	Good	
Umbricht, 1994 United States	Yes	Yes	Fair	
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	

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?
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)
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

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
Wirshing, 2002	Yes	Yes (tests within 2 1/2 years included)	Fair	
Zhao, 2002	Yes	Yes, 1 year	Fair	retrospective, 2-group cohort
Zhao, 2002	Yes	Yes	Fair	

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
Outpatients ***Aripiprazole***				
Vieta, 2005 England	RCT Multicenter	Patients aged 18-65 years, with DSM-IV diagnosis of bipolar I disorder, receiving in/out patient treatment for acute/mixed episode, Young Mania Rating Scale score of >20. Exclusion: presence of rapid-cyclng bipolar I disorder, duration of over 4 weeks of current manic episode, proven substance misuse, patient unreponsive to antipsychotics, significant risk of suicide, recent treatment with long-acting psychotropic medications (other than benzodiapines) within one day of randomization, fluoxetine treatment with 4 weeks of study, previous enrollment in aripiprazole study, shown intolerance to 15mg aripiprazole or 10mg haloperidol, lack of maintained effect after week 3 of study medication, hospitalization for manic or depressive symptoms, need for additional/increased doses of psychotropic medications, MADRS score <18, need for concomitant medication for symptomatic treatment or side-effects	Aripiprazole 15mg daily vs haloperidol 10mg daily, duration; 12 weeks	NR/1-3 days
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 cognitve 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
Outpatients ***Aripiprazole***			
Vieta, 2005 England	Lorazepam 4mg daily, oxazepam 30mg daily	Young Mania Rating Scale, CGI-BP and MADRS at baseline, and weeks 1, 2, 4, 6, 8, 10, 12. SAS, BAS, AIMS at weeks 2,3,6, 12. Vitals and lab tests and weeks 3,8,12.	Mean age: 41.8 years 38.3% Male
Sachs, 2006 United States	Lorazepam allowed on days 1-4(<6mg/dday), 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
Outpatients			
Aripiprazole			
Vieta, 2005 England	NR	NR/372/347	208/7/338
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
Outpatients ***Aripiprazole***		
Vieta, 2005 England	Overall response to treatment at 12 weeks: A: 49.7% vs H: 28.4%; p<0.001 YMRS: reduction of scores at 12 weeks: A: 19.9 vs H: 18.2; p=0.226 CGI-BP Severity reduction of scores at 12 weeks: A: 2.58 vs H: 2.27; p=0.095 MADRS reduction of scores at 12 weeks: A: 33% vs H: 37%	EPS Scale, patient report
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
Outpatients ***Aripiprazole***			
Vieta, 2005 England	EPS events reported: A: 24.0% vs H: 62.7% One patient discontinued haloperidol after suspected, drug-related liver damage Insomnia: A: 13.7% vs H: 7.1% Akathsia: A: 11.4% vs H: 23.1% Depression: A: 11.4% vs H: 14.2% Headache: A: 10.9% vs H: 11.8% Extrapyramidal syndrome: A: 9.1% vs H: 35.5% Tremor: A: 6.9% vs H: 10.1%	208; 116- O: 32 vs H: 84	
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
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, 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, 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, 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, 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 Simpson-Angus Rating Scale mean change (points): +0.48 vs -0.10; p≤0.05 Barnes Rating Scale mean change (points): +0.33 vs -0.11; p≤0.01 AIMS mean change (points): +0.01 vs -0.16; p=NS Weight gain (% patients ≥ 7% increase): 2 vs 0; population included in the weight analysis not cited; p=NS Serum prolactin mean change (ng/ml): -12.7 vs -7.2; p≤0.05 Significant increase in QTc interval (% patients): 0 vs 0	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
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 (eg, 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

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

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

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%).

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	

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 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, scizoaffective disorder. Psychotic suymptoms explained by other medical condition or substance abuse. Cocaine use Allergy/hypersensitivity to ariptizole or quinolinones, nueroleptic 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 randomised to ariipiprazole or placebo for 26 weeks	Stabilization 6-18 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
Keck, 2006 US Argentina and Mexico (76 centers)	Lorazepam and anticholingeric 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

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 US Argentina and Mexico (76 centers)	Current epidisode Mania 70% Mixed 30%	633 recruited 567 stabilization phase 161 entered RCT	94/ NR/ 161

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 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).	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

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 US Argentina and Mexico (76 centers)	Pacebo vs. aripiprazole % Any AE 69.9 vs. 74.0 Asthenia 8.4 vs. 7.8 Headache 16.9 vs. 7.8 Pain in extermities 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	Placebo vs. aripiprazole Total 66% vs. 50% due to AES 1% vs. 6%	

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
Olanzapine				
Tohen, 2002 USA and Canada	RCT DB	Bipolar disorder, manic or mixed episode, with or without psychotic features; at least 2 previous depressed, manic, or mixed episodes as well as a Young Mania Rating Scale12 (YMRS) total score of 16 or greater at visit 1 and visit 2 (2-7 days later); documented trial of treatment, with a therapeutic blood level of lithium (0.6-1.2 mmol/L) or valproate (50-125 µg/mL), for at least 2 weeks immediately prior to visit 1; showed inadequate response to monotherapy (YMRS total score >=16).	Olanzapine (flexible dose range of 5, 10, 15, or 20 mg/d) added to valproate or lithium or placebo added to valproate or lithium 6 weeks	2- to 7-day screening and washout 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
Olanzapine			
Tohen, 2002 USA and Canada	Benzodiazepines and anticholinergics	YMRS, HAMD-21, CGI-BP, assessed weekly	Mean age 40.6 years 48% male 85% 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
Olanzapine			
Tohen, 2002 USA and Canada	48% mixed episodes	501/NR/344	102/0/344

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Olanzapine		
Tohen, 2002 USA and Canada	Olanzapine vs. placebo change in YMRS 13.11 vs 9.10 P =0.003 Clinical response rates (>=50% improvement on YMRS) 67.7% vs 44.7% P < 0.001 Change in HAMD-21 4.89 vs 0.89 P < 0.001. Change in CGI-BP 1.2 vs 0.89 P = 0.04 Change in Total PANSS 12.9 vs 6.96 P = 0.003	Costart, Simpson-Angus Scale, the Barnes Akathisia Scale,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
Olanzapine			
Tohen, 2002 USA and Canada	Olanzapine vs. placebo Somnolence 51.5 vs 27 P < 0.001 Dry mouth 31.9 vs 7.8 P < 0.001 Weight gain 26.2 vs 7.0 P < 0.001 Increased appetite 23.6 vs 7.8 P < 0.001 Tremor 23.1 vs 13.0 P = 0.03 Asthenia 18.3 vs 13.0 P =0.28 Depression 17.9 vs 17.4 P > 0.99 Headache 15.7 vs 18.3 P = 0.54 Dizziness 13.5 vs 7.0 P = 0.07 Diarrhea 11.8 vs 14.8 P = 0.49 Nervousness 10.5 vs 14.8 P = 0.29 Thirst 10.0 vs 6.1 P = 0.31 Speech disorder 6.6 vs 0.9 P = 0.02 No statistically significant changes from baseline were seen in extrapyramidal symptoms	Total withdrawals 102 due to AE 27	

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, 2003a United States	DB RCT	Inclusion: 18–75 years and met the DSM-IV diagnostic criteria for a manic or mixed episode of bipolar disorder; baseline total score of at least 20 on the YMRS; Female patients of childbearing potential were required to use a medically accepted means of contraception. Exclusion: serious and unstable medical illness; DSM-IV substance dependence within the past 30 days (except nicotine or caffeine); documented history of intolerance to olanzapine or divalproex; treatment with lithium, an anticonvulsant, or an antipsychotic medication within 24 hours of randomization; treatment with clozapine within 4 weeks of randomization; and serious suicidal risk.	Olanzapine mean dose 16.2 mg/day Divalproex mean dose 1584.7 mg/day for 47 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, 2003a United States	Lorazepem and benztriopine	YMRS, HAMD-21, CGI-BP, PANSS daily during the first week, weekly from weeks 1 to 5, biweekly from weeks 5 to 11, monthly from weeks 11 to 23, and bimonthly from weeks 23 to 47.	Mean age 41 years 57.4% female 80.9% 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
Tohen, 2003a United States	Mean duration of condition 18.2 yrs Duration of current episode 47.8 days Mean YMRS 27.7	NR/NR/251	212/25/248

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Tohen, 2003a United States	Olanzapine vs. Divalproex change in YMRS 15.38 vs 12.5 P =0.03 Clinical remission rates 56.8% vs 45.5% P = 0.10 Change in HAMD-21 3.78 vs 1.59 P = 0.08 Change in CGI-BP 1.98 vs 1.7 P = 0.06 Change in Total PANSS 12.11 vs 8.87 P = 0.25	Assessing adverse events, laboratory values, ECGs, vital signs, weight change, and extrapyramidal symptoms

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, 2003a United States	Olanzapine vs. Divalproex (%) Nausea 16 vs 31.7 P = 0.005 Depression 34.4 vs 30.2 P = 0.51 Headache 26.4 vs 27 P = 1.00 Somnolence 46.4 vs 24.6 P < 0.001 Nervousness 12 vs. 22.2P = 0.05 Pain 18.4 vs 21.4 P = 0.64 Diarrhea10.4 vs 19.0 P = 0.08 Asthenia 23.2 vs 18.3 P = 0.36 Vomiting 13.6 vs18.3 P = 0.39 Anxiety 12.8 vs 17.5 P = 0.38 Dizziness 18.4 vs 16.7 P = 0.75 Rhinitis 12.8 vs 15.9 P = 0.59 Insomnia 8.0 vs 15.9 P = 0.08 Dyspepsia 16.8 vs 15.1 P = 0.74 Constipation 15.2 vs 15.1 P = 1.00 Agitation 16 vs 13.5 P = 0.60 Weight gain 7% or more 24.8 vs 11.9 P = 0.01 Tremor 12.0 vs 11.1 P = 0.85 Apathy 12 vs 11.1 P = 0.85 rash 11.2 vs 11.1 P = 1.00 Pharangytis 10.4 vs 11.1 P = 1.00 Back pain 7.2 vs 11.1 P = 0.39 Abnormal thinking 6.4 vs 11.1 P = 0.27 Manic reaction 3.2 vs 10.3 P = 0.05 Dry mouth 34.4 vs 7.1 P < 0.001 Myalgia 10.4 vs 7.1 P = 0.39 Rectal disorder 0 vs 5.6 P = 0.02 Increased appetite 13.6 vs 5.6 P = 0.04 Akathisia 9.6 vs 1.6 P = 0.006 Abnormal result on liver function test 4.0 vs 0 P < 0.001 No statistically significant changes from baseline were seen in extrapyramidal symptoms	Total withdrawals 212 due to AE 56	

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, 2003b Western Europe, South Africa, and North and South America	RCT DB	18 years and older; met the DSM-IV13 criteria for bipolar I disorder manic or mixed type (with or without psychotic features), and had a baseline Young-Mania Rating Scale (YMRS) score of 20 or higher. Patients were excluded if they had a serious, unstable medical illness, had DSM-IV substance dependence (except nicotine or caffeine) within the past 30 days, or were considered a serious risk of suicide.	Olanzapine (5, 10, 15, or 20 mg/d) or haloperidol (3, 5, 10, or 15 mg/d) 12 weeks total 6 weeks short-term and showed at least a 1-point improvement from baseline in CGI-BP continued for additional 6 weeks	2 to 7 day screening period
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 µlu/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
Maina, 2007 Italy	Open-label RCT	Diagnosis of bipolar disorder, manic or hypomanic episode;Young Mania Rating Scale (YMRS) total score≥16 and HAMD≤7, to exclude patients with mixed episodes; a documented trial of treatment with lithium of at least 1 year, with a therapeutic blood level (0.6–1.2 mmol/L) at entry. Exclusion - administered other concurrent drugs, with the exception of benzodiazepines, during the index manic or hypomanic episode.	Valproate (500–1500 mg/day) or olanzapine (7.5–15.0 mg/day) add-on to lithium for up to 8 weeks	NR- but previous trmt with lithium established

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, 2003b Western Europe, South Africa, and North and South America	Concomitant medications with primary central nervous system activity were restricted to benzodiazepines (lorazepam up to 4 mg/d for a maximum of 14 cumulative days); anticholinergics (biperiden or benztropine mesylate up to 6 mg/d)	YMRS, HAMD-21, SF-36 at baseline, weeks 6 and 12	40 years old 60.3% female Ethnicity 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
Maina, 2007 Italy	None	YMRS, Clinical Global Impressions Severity and Improvement from baseline to 8 weeks. Weekly Response to treatment was defined as a mean reduction of ≥50% in YMRS total score and remission as a YMRS total score≤12	Mean age 46.5 years 57% 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, 2003b Western Europe, South Africa, and North and South America	94.5% manic index episode 57.4% experiencing psychotic features 79% hospitalized	498/NR/453	197/NR/453
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
Maina, 2007 Italy	Mean duration of illness (years): 17.1	NR/NR/21	0/0/21

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Tohen, 2003b Western Europe, South Africa, and North and South America	Olanzapine vs haloperidol 6 weeks Rates of remission (YMRS of <=12 and 21-item HAMD-21 of <=8) 52.1% vs 46.1% P = 0.15. 12 weeks Change in YMRS 26.5 vs 26.8 P = 0.72 Change in HAMD-21 2.6 vs 1.7 P = 0.24	Nondirected, open-ended questioning, spontaneous report, and clinical observation.
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
Maina, 2007 Italy	Change in YMRS valproate vs. olanzapine −17.58 vs −20.15, p=0.367 Response, n (%) valproate 6 (66.7) vs. olanzapine 10 (83.3) Remission, n (%) valproate 5 (55.6) vs. olanzapine7 (58.3)	Clinical interview

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, 2003b Western Europe, South Africa, and North and South America	Haloperidol vs Olanzapine % Somnolence 8.7 vs 15 P = 0.04 Weight gain 4.1 vs 13.7 P < 0.001 Infection 1.4 vs 5.1 P = 0.03 Dizziness 0.9 vs 4.3 P = 0.004 Fever 0 vs 4.3 P = 0.002 Increased salivation 7.3 vs 1.3 P = 0.002 Change from baseline at week 12 in EPS Simpson-Angus 1.65 vs -0.59 P < 00.001 Barnes Akathisia Scale 0.45 vs -0.13 P< 0.001 AIMS 0.19 vs -0.14 P = 0.03	Total withdrawals 197 due to AE 44	
Amsterdam, 2005 United States	NR	Total with drawals14 (41%) 2 for Aes	
Maina, 2007 Italy	Valproate vs. olanzapine Somnolence: 11.1% [1/9] vs. 25.0% [3/12] Tremor 22.2% [2/9] vs. 16.7% [2/12] Weight gain: 11.1% [1/9] vs. 8.3% [1/12] Headache: 11.1% [1/9] vs. 8.3% [1/12]	0/0	

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
Tohen, 2003 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
Shi, 2004 International QoL analysis of Tohen 2003 (see above)	RCT, DB, placebo-controlled, Multicenter	This double-blind trial involved inpatients and outpatients in an acute depressive episode of bipolar I disorder. Before randomization, pts underwent a screening period (min 2 days, max 14 days). Men and women aged > 18 years were eligible for enrollment if they met the DSM-IV criteria for bipolar I disorder, most recent episode depressed, and their diagnosis was confirmed by the Structured Clinical Interview for the DSM-IV Patient Version. Pts were required to have a score of >20 on the Montgomery-Asberg Depression Rating Scale (MADRS) at the screening visit and on the day of randomization (baseline). Pts were also required to have a history of > 1 previous manic or mixed episode of sufficient severity to have required treatment with a mood stabilizer or 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	See Tohen 2003

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 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, HAM-A Clinical visits conducted at weeks 1, 2, 3, 4, 6, and 8	Mean age=41.8 63% female 82.6% white
Shi, 2004 International QoL analysis of Tohen 2003 (see above)	See Tohen 2003	Health-related Quality of Life (HRQOL) outcomes using the SF-36 and the QLDS (Quality of Life in Depression Scale) assessed at baseline and week 8 (or post-baseline visit if a patient was discontinued from study)	Mean age: 41 years 35.1% 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, 2003 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
Shi, 2004 International QoL analysis of Tohen 2003 (see above)	see Tohen 2003	NR/1072/833 Placebo n=377 Olanzapine n=370 Olanzapine+fluoxetine n=87	454/833(54.5%) withdrawn 57/833(6.8%) lost to follow-up 788/833 (94.6%) analyzed For SF-36 data, 573/833 (68.8%) analyzed For QLDS data, 546/833 (65.5%) 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 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	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
Shi, 2004 International QoL analysis of Tohen 2003 (see above)	For SF-36 mean change in score over a total of 8 different dimensions, p <0.005 for the listed dimensions Olanzapine > placebo : mental health, role-emotional, and social functioning; and on the Mental Component score OFC > placebo: general health, mental health, role-emotional, social functioning, and vitality; and on both the Physical and Mental Component scores OFC> Olanzapine : general health, mental health, role-emotional, social functioning, and vitality; and on both the Physical and Mental Component scores For the QLDS total score, mean change in score (SD) reported as olanzapine vs OFC vs placebo: -6.26 (10.06) vs -11.30(10.59) vs -5.52 (10.10), p=NS for olanzapine vs placebo p<0.001 for OFC vs placebo and for OFC vs olanzapine	See Tohen 2003

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 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)	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	
Shi, 2004 International QoL analysis of Tohen 2003 (see above)	See Tohen 2003	See Tohen 2003	

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
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
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
Namjoshi, 2004 United States	NR	Young Mania Rating Scale (Y-MRS), Hamiliton 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
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)
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
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)
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
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%)	
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
Tohen, 2006 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
Tohen, 2005 Western Europe, Canada, South Africa, Israel, Australia, and New Zealand	Open RCT Multicenter	Patients aged 18 years and older, meeting DSM-IV ciriteria for bipolar disorder as determined with Structured Clinical Interview for DSM-IV, patient version, with symptomatic remission criteria, Young Mania Rating Scale total score >20 at baseline, history of at least two manic or mixed episodes within the last 6 years. Exclusion: serious, unstable medical illness, met DSM-IV substance dependence criteria within past 30 days, treatment with a depot neuroleptic within 6 weeks of randomization, serious suicide risk, history of intolerance, lack of response or adverse event to to lithium or olanzapine.	Olanzapine: 11.9 mg vs 11.02.7mg lithium	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
Tohen, 2006 Unied States and Romania	NR	Young Mania Rating Scale, Hamilton Depression Rating Scale	Mean age: 40.4 years 39% Male Ethnicity NR
Tohen, 2005 Western Europe, Canada, South Africa, Israel, Australia, and New Zealand	Biperiden or benzotropine mesylate, >6 mg/day; trihexyphenidyl, < 12 mg/day	Young Mania Rating Scale, 1-item Hamilton depression scale, Simpson-Angus Rating Scale (SAR), Barnes Rating Scale for Drug-Induced Akathisia, Abnomral Involuntary Movement Scale (AIMS)	Mean age: 42.4 Years 53.2% Female 99.3% 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
Tohen, 2006 Unied States and Romania	Median Length of current episode: O: 29 days vs L: 27.5 days	931/731/361	90/24/361
Tohen, 2005 Western Europe, Canada, South Africa, Israel, Australia, and New Zealand	Length of current episode (days): O: 37.7 vs L: 37.0 Time in remission before randomization (days): O: 19.7 vs L: 20.6	0/543/431	0/0/171

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Tohen, 2006 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	Laboratory tests, patient report
Tohen, 2005 Western Europe, Canada, South Africa, Israel, Australia, and New Zealand	Symptomatic recurrence of any mood episode follwing remission of mania/depression: O: 30.0% vs L: 38.8% Number of patients hospitalized for mmod episode during treatment period: O: 14.3% vs L: 22.9%; p<0.03 Treatment-emergent EPS symptoms reported: Parkinsonism (SAS): O: 3.4% vs L: 2.8%; p=1.0 Dyskinesia (AIMS): O: 1.5% vs L: 1.0%; p=0.69 Akasthisia (Barnes Rating Scale for Drug-Indiced Akathisia): O: 0% vs L: 2%	One patient committed suicide during treatment period from lithium group

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, 2006 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%	90;17	
Tohen, 2005 Western Europe, Canada, South Africa, Israel, Australia, and New Zealand	Adverse events reported, > 5%: Depression not otherwise specified: O: 20.7% vs L: 11.7%; p=0.01 Weight gain: 10.3% Tremor: 9.8% Sedation: 7.2% Somnolence: 6.8% Insomnia: 5%	0;96	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name ***Quetiapine***	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
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

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name ***Quetiapine***	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
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

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
Quetiapine			
Altamura, 2003 Italy	Bipolar I Disorder=13 (46.4%) Bipolar II Disorder=15(53.6%)	NR/NR/28	nr/nr/nr
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)

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Quetiapine		
Altamura, 2003 Italy	Quetiapine=Mood Stabilizers in YMRS, BPRS, HAM-D and CGI scores (data nr)	NR
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

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
Quetiapine			
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	
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	

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

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

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)

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

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 SAS and BARS mean changes: QTP=PBO, ns (data nr)	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	

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
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

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
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

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)
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)

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 (pooed 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
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.

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	
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	

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,

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

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

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.

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%)	

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 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 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 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 ments at days 1, 4, 7, 14, 21, 28, 42, 56, 70, and 84 Safety evaluations were based on reports of AEs, trought 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 comparisions 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
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
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
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
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
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
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
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.
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
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	
Thase, 2006 USA BOLDER 2	Palacebo 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
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

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

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

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.

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%)	

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
Risperidone				
Harvey, 2007 USA	Randomized, DB cross-over	18-55 years oldDSM-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
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
Risperidone			
Harvey, 2007 USA	Yes if they were stable for the proceeding 8 weeks.	NA	Mran age 40.9 years 71% male 32% white 61% black 7% 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
Risperidone			
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
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
Risperidone		
Harvey, 2007 USA	see adverse events	Assumed to be patient reported, not specified
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
Risperidone			
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	
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
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
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
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
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
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
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
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
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
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	
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
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

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

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

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

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%)	

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 Parethesias: 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
Barekatain, 2005 Iran	DB RCT Inpatient psychiatric hospital	Inclusion- 18-65 years old with BMD-I most recent episode manic, hospitalized for treatment minimum score of 20 and maximum score of 50 on the Young Mania Rating Scale (YMRS) Exclusion- another DSM-IV axis I diagnosis except substance abuse; use of mood stabilizers within 72 hours; known sensitivity to risperidone, lithium or sodium valproate; history of severe EPS and history of response to another treatment regimens in past episodes. Also, laboratory values (liver, renal and thyroid function tests) outside the normal range; history of clinically significant medical diseases; pregnancy; lactation and childbearing potential (without adequate contraception)	Sodium valproate 20 mg/d plus risperidone or lithium. In both groups, 14 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
Barekatain, 2005 Iran	Oral clonazepam or lorazepam	Change in the mean of YMRS scores from baseline to endpoint. "YMRS response", (a reduction of 50% or more in YMRS scores) and "YMRS remission" at baseline and day 14	Mean age 30.6 years 54% 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
Barekatain, 2005 Iran	Duration of disorder 5.6 years	59/NR/46	14/NR/32

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Barekatain, 2005 Iran	Valproate/risperidone vs. valproate/lithium YMRS at 14th day n=32 19.6(5.5) vs. 16.3(6.6) P=0.004 YMRS remission (%) 75 vs. 37.5 P = 0.073 YMRS response (%) 93.7 vs. 43.7 P = 0.006 CGI severity CHANGE between: 14th day and baseline 2.6(1.0) vs. 1.6(1.1) P=0.007 CGI global improvement response (%) 68.75 vs. 31.25 P = 0.015	Vital signs, physical examination and direct questions

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
Barekatain, 2005 Iran	valproate/risperidone vs. valproate/lithium Somnolence 26.1 vs. 27.2 Tremor 21.7 vs. 9.0 Nausea 17.4 vs. 27.2 Dizziness 17.4 vs. 13.6 Vomiting 8.7 vs. 13.6 Dyspepsia 8.7 vs. 27.2 Diarrhea 4.3 vs. 9.0 Extra pyramidal 4.3 vs. 0.0 Urinary frequency 0.0 vs. 4.5	Withdrawals 14 (30%) due to Aes 1 maybe?	completers analysis 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
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
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
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
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 rispeidone 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
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 Setting	Study design	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Inpatients				
Clozapine				
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
Olanzapine				
Berk, 1999 South Africa	RCT, DB	Thirty pts aged 18-65 years who were admitted with an acute manic episode were selected for the study. To be included, the patients were required to meet DSM-IV criteria for bipolar disorder, manic phase.	Olanzapine 10 mg/day Lithium carbonate 800 mg/day Duration: 4 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
Inpatients			
Clozapine			
Barbini, 1997 Italy	NR	Young Rating Scale of Mania (YRSM)	Mean age: 36.6 years 37% male Ethnicity NR
Olanzapine			
Berk, 1999 South Africa	Lorazepam 4-12 mg if necessary	Mania Scale (MAS) Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression (CGI) Global Assessment Functioning Scale (GAF)	Mean age: 30.7 years Gender unclear 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
Inpatients			
Clozapine			
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
Olanzapine			
Berk, 1999 South Africa	Olanzapine vs lithium Mean (range) episode duration: 19.3(8-38) vs 15.06(7-29) Mean (range) no. manic episodes: 3.4(1-8) vs 2.13(0-5) Mean (range) no. depressive episodes: 0.7(0-3) vs 0.26(0-1) Mean (range) no. previous admissions: 2.9(1-11) vs 1.6(1-4)	NR/NR/30	4/NR/30

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Inpatients		
Clozapine		
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
Olanzapine		
Berk, 1999 South Africa	Baseline vs endpoint: BPRS: olanzapine: 53.3 vs 28.0, p=0.0002 lithium: 46.8 vs 28.2, p=0.0002 olanzapine vs lithium at baseline, p=0.077 olanzapine vs lithium at endpoint, p=0.439 CGI-severity scale: olanzapine: 4.67 vs 2.29 lithium: 4.67 vs 2.83 olanzapine vs lithium at baseline, p=1.000 olanzapine vs lithium at endpoint, p=0.025 % change from baseline: olanzapine vs lithium = 48.6% vs 38.3, p=0.018 CGI-improvement scale: olanzapine: 4.27 vs 2.36 lithium: 4.27 vs 2.75 olanzapine vs lithium at baseline, p=0.808 olanzapine vs lithium at endpoint, p=0.163 GAF: olanzapine vs lithium at endpoint: 57.9 vs 56.2, p=0.583 MAS: olanzapine: 31.7 vs 10.2 lithium: 31.6 vs 13.2 olanzapine vs lithium at baseline, 0.900 olanzapine vs lithium at endpoint, 0.315	"Side effects were noted" EPS: Simpson-Angus Scale (SAS) and Barnes Akathisia 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
Inpatients			
Clozapine			
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	
Olanzapine			
Berk, 1999 South Africa	SAS: olanzapine: 0.53 vs 0.64 lithium: 2.33 vs 2.83 olanzapine vs lithium at baseline, 0.204 olanzapine vs lithium at endpoint, 0.185 lorazepam used (mg): olanzapine vs lithium = 69.1 vs 74.6, p=0.429 biperidin used (mg): olanzapine vs lithium = 6.33 vs 0.66, p=0.962 Barnes Akathisia Scale: no treatment emergent akathisia	Olanzapine vs lithium Total withdrawals: 1 vs 3 Withdrawals due to AEs: 1 vs 1	There was a third limb of the study using lamotrigine, that data is not presented here.

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, benzotropine 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
Moreno, 2007 Brazil	RCT,DB	DSM-IV's (22) criteria for bipolar disorder, acute manic phase, with or without psychotic characteristics; had not switched from a depression phase to mania, or from a mania phase to depression, within 1 month before or after the PSG procedure. YMRS had to score higher than 20 on the occasion of bothvisits 1 and 2	Olanzapine 15 mg/day Haloperidol 10 mg/day for 31-51 days, about 6 weeks	4 day washout
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

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
Moreno, 2007 Brazil	NR or none	One-night polysomnographic evaluation was performed before and after ;Young Mania Rating Scale (YMRS) and the Clinical Global Impressions - Bipolar version (CGI-BP).	Mean age 38.8 years 25% male Ehnicity NR
Perlis, 2007 USA	Benztropine mesylate and loazepam	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

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
Moreno, 2007 Brazil	Means: Previous manic episodes (#): 5.7 Manic episodes in past year (#): 0.4 Age at onset of manic symptoms: 30.3 Previous depressive episodes (#): 5.4 Depressive episodes in past year (#): 0.7 Age at onset of depressive symptoms (yrs): 35.6 Previous admissions (#): 2.6 Psychotic features during mood episodes (# patients): 5	NR/19/12	NR/NR/12
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

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name	Results	Method of adverse effects assessment
Moreno, 2007 Brazil	Scale Haloperidol group Olanzapine group Before treatment After treatment Before treatment After treatment YMRS 30.6 ± 8.6 4.8 ± 10.7* 30.6 ± 5.0 10.4 ± 13.8* CGI-BP 13.0 ± 2.0 4.6 ± 3.6* 11.3 ± 1.8 6.4 ± 3.0* *P < 0.05 compared to pre-treatment olanzapine- statistically significant time-drug interaction effects on sleep continuity measures were observed: sleep efficiency (mean ± SEM pre-treatment value: 6.7 ± 20.3%; after-treatment: 85.7 ± 10.9%), total wake time (pre-treatment: 140.0 ± 92.5 min; aftertreatment: 55.2 ± 44.2 min), and wake time after sleep onset (pretreatment: 109.7 ± 70.8 min; after-treatment: 32.2 ± 20.7 min). Conversely, improvement of polysomnographic measures was not observed for the haloperidol group (P > 0.05).	NR
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.

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
Moreno, 2007 Brazil	NR	0 withdrawals	
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	

Evidence Table 8. Randomized controlled trials in patients with bipolar I disorder

Author, year Country Trial name Setting	Study design	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
Risperidone				
Segal, 1998 South Africa	RCT, DB	The patients were required to meet DSM-IV criteria for bipolar disorder, manic phase, on as structured clinical interview	risperidone 6 mg/day haloperidol 10 mg/day lithium 800-1200 mg/day Duration: 4 weeks	NR/ NR
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
Risperidone			
Segal, 1998 South Africa	Lorazepam was given when necessary to control aggression	Primary outcome measure: Mania Rating Scale (MRS) Secondary outcome measures: Brief Psychiatric Rating Scale (BPRS) Clinical Global Impression (CGI) Global Assessment of Functioning Scale (GAF)	Mean age: 33.6 years 22.2% male Ethnicity 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
Risperidone			
Segal, 1998 South Africa	NR	NR/NR/45	NR/NR/45
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
Risperidone		
Segal, 1998 South Africa	risperidone vs haloperidol vs lithium, p value BPRS: baseline: 17.6 vs 15.2 vs 17.4, NS endpoint: 6.5 vs 4.9 vs 9.1, NS MRS: baseline: 28.6 vs 24.8 vs 28.4, NS endpoint: 12.4 vs 10.2 vs 15.7, NS all three groups have significant improvement compared with baseline, p<0.001 CGI: baseline: 4.0 vs 3.6 vs 3.7, NS endpoint: 1.9 vs 1.6 vs 2.4, NS GAF: baseline: 33.8 vs 40.2 vs 32.6, p=0.18 endpoint: 59 vs 63.4 vs 54.6, p=0.46	Simpson-Angus Scale (SAS)
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
Risperidone			
Segal, 1998 South Africa	risperidone vs haloperidol vs lithium, p value SAS: baseline: 1.33 vs 0.46 vs 0.66, NS endpoint: 3.93 vs 2.66 vs 0.4, p=0.01 risperidol vs haloperidol, NS orphenadrine used; risperidone: 100 mg haloperidol: 229.6 mg risperidone vs haloperidol, NS seclusion required: endpoint: 8(53%) vs 8(53%) vs 11(73%)	NR	
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 *Ziprasidone*	Study design Setting	Eligibility criteria	Therapy type Interventions Duration	Run-in/washout period
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 placeb	Run-in 3-10 days
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 bilater 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 ***Ziprasidone***	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
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
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 *Ziprasidone*	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
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
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
Ziprasidone		
Potkin, 2005 United States, Brazil, and Mexico.	Ziprasidone vs. placebo Baseline-to-endpoint mean changes MRS scores -11.1 fvs. -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)
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, ziprazadone 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
Ziprasidone			
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	
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
Intramuscular				
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
Intramuscular			
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 (lLOCF 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), YoungMania 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
Intramuscular			
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
Intramuscular		
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 $\leq$ 0.01 vs placebo. yP $\leq$ 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
Intramuscular			
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 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 2 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	Olaznapine 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 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

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	Post-randomization exclusions	Quality rating
Altamura, 2003	NR NR NR NR	NR NR	Unclear	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	No	Poor

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

External Validity

Author, year	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ washout
Altamura, 2003	NR/NR/28	Presence of major mood episodes not in partial or full remission; concomitant psychotropic medication at the time of the beginning of the study, with the exception of previously stabilized (for at least 2 weeks) dosages of benzodiazepines (not to exceed 5 mg/day diazepam equivalents); pregnancy or lactations; serious medical conditions contraindicating the use of quetiapine or any mood stabilizers; no history of ever using mood stabilizers	No/No
Amsterdam, 2005	41/NR/34	Current alcohol or substance abuse, hx of alcohol or substance abuse within 3 mos, nonresponse to fluoxetine within current MDE, sensitivity to fluoxetine or olanzapine, pregnant or nursing women, unstable medical conditions, thyrotropin level ≥5 micolu/mL; presence of clinically significant cardiac dz, hepatic dz, renal dz, malignancy, CNS disorder, use of chemotherapy, use of OTC like St. John's Wort, use of tranquilizers, barbiturates, other sedatives and hypnotics	Unclear/Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Class naïve patients only	Control group standard of care	Funding	Relevance	Comments
Altamura, 2003	Naïve to mood stabilizers	Yes	NR	Only to patients with no history of mood stabilizer use and who were in partial- or full-remission	
Amsterdam, 2005	No	No (PCT)	NR	Yes	Is 8 weeks long enough time to assess whether fluoxetine doesn't induce mania?

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?
Barekatain, 2005	Method not described	NR	No; differences in gender distribution, presence of substance abuse, hospitalizations	Yes	Unclear, reported as DB	Unclear, reported as DB	Unclear, reported as DB
Brecher, 2003 Poster	NR	NR	Yes	Yes	Yes	Yes	Yes
Calabrese, 2004 Poster	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	Post-randomization exclusions	Quality rating
Barekatain, 2005	Yes NR NR NR	~30% discontued before end of trial Differential: low	No; did not specify which population they used for their analyses	Yes; patients who missed before fourth day of study (?) or whose management was changed due to problems were excluded from analysis	Poor
Brecher, 2003 Poster	Yes NR NR NR	No No	LOCF	No	Fair
Calabrese, 2004 Poster	Yes NR NR NR	NR NR	LOCF	No	Fair

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

External Validity

Author, year	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ washout
Barekatain, 2005	59/NR/46	Another DSM-IV Axis I diagnosis except substance abuse; use of mood stabilizers within 72 hrs before hospitalization; sensitivity to risperidone, lithium or sodium valproate, hx of severe EPS and hx of response to another txmt regimen in past episodes, abnormal labs for (LFTs, renal, thyroid function), hx of clinically significant medical dz, pregnancy, lactation,childbearing potential without adequate contraception	No
Brecher, 2003 Poster	NR/NR/302	Hospitalized for weeks for the index manic episode; meeting SDM-IV criteria for rapid cycling or current mixed episode; index manic episode as direct consequence of medical condition, treatment, or substance abuse; known intolerance or lack of response to QTP, HPL or clozapine; use of antihypertensives (unless stable dose for ≥ month), clozapine, > 4 mg/d lorazepam, antidepressants, thioridazine, or potent cytochrome P450 inducers/inhibitors within specified time intervals of randomization; substance/alcohol dependence or electroconvulsive therapy within 1 month of randomization	NR/NR
Calabrese, 2004 Poster	838/NR/542	Other Axis I disorders	NR/NR

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Class naïve patients only	Control group standard of care	Funding	Relevance	Comments
Barekatain, 2005	Unclear	Unclear	NR	Yes	
Brecher, 2003 Poster	Unclear	Yes	AstraZeneca	Yes	
Calabrese, 2004 Poster	Unclear	Yes	AstraZeneca	Yes	

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?
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
Keck, 2003	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	Post-randomization exclusions	Quality rating
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	No	Fair
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 .	No	Fair
Keck, 2003	Yes NR NR NR	NR NR	No	No	Fair

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

External Validity

Author, year	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ washout
Harvey, 2007	NR/NR/30	Current use of BZPs, prescription herbal sleep agents, antihistamines; current symptoms of depression (Montgomery score > 12); current diagnoses of MDD, mania, hypomania, psychosis, dysthymia, or catatomic behaviors	NR/Yes (6-14 days between cross-over periods)
Hirschfeld, 2004	337/NR/262	Baseline YMRS score was ≥ 25% lower than the screening score; diagnosis of a mixed episode, schizoaffective disorder, borderline or antisocial personality disorder, seizure disorder, a history of substance dependence within 3 months of the screening, or were considered to be at significant risk for suicidal or violent behavior during the course of the trial	No/Yes
Keck, 2003	NR/NR/262	Patients were excluded from the study if they had delirium, dementia, amnestic or other cognitive disorders, schizophrenia, or schizoaffective disorder or if they were experiencing their first manic episode; duration of current mania > 4 weeks; nonresponse to clozapine; probable need for prohibited concomitant therapy; use of psychoactive substances or a substance use disorder; serum concentrations of lithium > 0.6 mmol/liter or divalproex sodium > 50 µg/ml at screening; significant risk of committing suicide or homicide; history of neuroleptic malignant syndrome or seizure disorder	No/Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Class naïve patients only	Control group standard of care	Funding	Relevance	Comments
Harvey, 2007	NR	Yes	Ortho-McNeil	Yes (see comments)	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	No	Yes	Johnson & Johnson Pharmaceutical Research and Development, LLC	Yes	
Keck, 2003	No	Yes	Bristol-Myers Squibb and Otsuka Pharmaceuticals	Yes	

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?
Keck, 2006	Method not described	NR	No; more males were randomized to aripiprizole 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
Maina, 2007	Method not described	NR	Yes	Yes	No, open-label	No, open-label	No, open-label

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	Post-randomization exclusions	Quality rating
Keck, 2006	Yes NR NR NR	58.4% withdrew Differential: ~16% difference between placebo and aripirazole arm	Yes	No	Fair
Khanna, 2003	Yes NR NR NR	No No	LOCF	No	Fair
Maina, 2007	Yes NR NR NR	No patients were discontinued	Yes	No	Fair

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

External Validity

Author, year	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ washout
Keck, 2006	633/NR/161 entered DB-phase	Hx of symptoms of a cognitive disorder, schizophrenia, schizoaffective disorder, psychotic symptoms better explained by another medical condition or attributed to substance abuse; those unresponsive to clozapine psychoactive or substance abuse disorder, positive u-tox for cocaine, lithium, divalproex; sensitivity to aripiprazole or quinolones, hx of NMS, sezure disorder, ECT in past 2 mos, another investigational drug in past month; patients were excluded from the DB-phase if they were noncompliant with study med or were in significant violation of protocol during stabilization phase	Yes (Run-in is referred to as "Stabilization period" of 3-weeks Washout-NR
Khanna, 2003	NR/NR/291	DSM-IV criteria for schizoaffective disorder, rapid cycling bipolar disorder, or borderline or antisocial personality disorder; substance dependence within the last 3 months; significant risk of suicide or violent behavior; pregnant or nursing; history of other unstable illness; a ≥ 25% decrease in their YMRS score from screening baseline; treatment with an antidepressant within 4 weeks of screening	NR/Washout details unclear
Maina, 2007	NR/NR/21	No mixed episodes of BPAD; administered other concurrent medications other than BZPs during the index manic or hypomanic episodes	NR

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Class naïve patients only	Control group standard of care	Funding	Relevance	Comments
Keck, 2006	No	No (PCT)	Bristol-Myers Squibb and Otsuka Pharmaceuticals	Yes	
Khanna, 2003	Unclear	Yes	Janssen Pharmaceutica Products, LP	Yes to "severe" patient population	
Maina, 2007	NR	Yes	NR	Yes	

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?
Moreno, 2007	Method not described	Patients were 'randomly' and 'consecutively' assigned	No; there were numeric differences in gender distribution, subjects in haloperidol arm had higher number of previous manic episodes, subjects in olanzapine arm had higher number of depressive episodes; all women enrolled in haloperidol arm had psychotic features during mood episodes	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

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	Post-randomization exclusions	Quality rating
Moreno, 2007	Yes NR NR Inadequate washout period for 8 patients	NR NR	Yes (12/12)	No	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	No	Poor
Paulsson, 2003	Yes NR NR NR	No No	No, 2 (0.6%) excluded for unspecified reasons	No	Fair

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

External Validity

Author, year	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ washout
Moreno, 2007	19/NR/12	Current or hx of substance abuse, serious general medical conditions or neurological diseases, primary sleep disorder	NR/Yes (washout duration inadequate--should be 2 weeks but was 4-days)
Nierenberg, 2006	67/NR/66	Hx of nonresponse to, intolerance of, or any medical contraindications to at least 2 of the study meds; diagnosis of mixed episode or hypomania or current substance abuse or dependence	NR/NR
Paulsson, 2003	NR/NR/302	Hospitalized for ≥ 3 week for the index manic episode; meeting DSM-IV criteria for rapid cycling or current mixed episode; index manic episode as direct consequence of medical condition, treatment or substance abuse; known intolerance or lack of response to QTP, Li, or clozapine; use of antihypertensives (unless stable dose for ≥ 1 month), clozapine, >4 mg/d lorazepam, antidepressants, thioridazine, or potent cytochrome P450 inducers/in inhibitors within specified time intervals of randomization; substance/alcohol dependence or ECG therapy within 1 month of randomization	NR/NR

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Class naïve patients only	Control group standard of care	Funding	Relevance	Comments
Moreno, 2007	NR	No	NR	Yes	
Nierenberg, 2006	No	No	NIMH	Yes	
Paulsson, 2003	Unclear	Yes	AstraZeneca	Yes	

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?
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
Sachs, 2004	NR	NR	Yes	Yes	Yes	Yes	Yes
Sachs, 2005	NR	NR	Yes	Yes	NR	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	Post-randomization exclusions	Quality rating
Perlis, 2006	Yes NR NR NR	Yes reported; > in olanzapine group (21.3%) vs. risperidone group (33%) (p= 0.019) Differential, not high	Yes	NR	Fair
Potkin, 2005	Yes NR NR NR	41% discontinued study overall 39% ziprasidone 46% placebo	Yes; LOCF for missing data	No	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)	No	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	One patient excluded from efficacy analysis due to early discontinuation	Fair

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

External Validity

Author, year	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ washout
Perlis, 2006	NR/329/329	Serious suidcide risk, DSM-IV substance dependence within the previous 2 months (except nicotine and caffeine), current hospitalization duration greater than greater than 3 weeks prior to the initial visit, greater than or equal to 90 day duration of current manic or mixed episode, or documented history of failure to respond during an adequate period of treatment with olanzapine or risperidone for acute mania.	Yes/Yes
Potkin, 2005	280/NR/206	Schizophrenia/schizoaffetive disorder, Type 1 BPAD with current depression, psychoative substance abuse/dependence in past 2 mos, substance-induced psychotic disorder or behavioral disturbance; received clozapine 12 weeks prior, baseline lithium >0.2 mEq/L, valproate >50 mcg/mL, carbamazepine >4 mcg/mL; mental retardation; imminent risk for suicide or homicide	Yes/Yes
Sachs, 2004	NR/NR/191	Pregnant or lactating women and those of chid-bearing potential not using a reliable method of contraception were excluded from participating in the study. Patients whose current manic episode was due to a medical condition were also excluded. Other patients who were excluded were those meeting DSM-IV criteria for rapid cycling, those who had required hospitalization for 3 or more weeks for the index manic episode, or those with known intolerance or lack of response to QTP or clozapine. The continuous daily use of benzodiazepines, in excess of 4 mg/day of lorazepam or the equivalent, was also not allowed during the month preceding screening. Patients requiring the use of antihypertensive medications, unless stable for at elast 1 month, or the use of antidepressants during the screening period (day -7 to 1) or within a period of five half-lives of the drug prior to study randomization, were also ineligible. The use of depot hloperidol and fluphenazine (within one injection cycle), and certain cytochrome P450 3a4 inhibitors and inducers, thioridazine, or any experiemental drugs within 2 weeks prior to randomization was not permitted. Also excluded were patients who had a of clinically significant medical disease.	NR/NR
Sachs, 2005	NR/NR/272	Diagnosis of delerium, dementia, amnestic or other cognitive disorders, schizophrenia or schizoaffective disorder; first manic episode; current manic episode >4 wks; unresponsive to clozapine; possibility that patient would require prohibited concomitant therapy; use of psychoactive substances or a substance use disorder; serum concentrations of lithium ≥0.6mmol/L or divalproex sodium ≥50ug/mL; significant risk of suicide or homicide; history of neuroleptic malignant syndrome or seizure disorder; clinicall significant abnormal laboratory test results, vital signs or ECG; previous enrollment in an aripiprazole trial.	NR/NR

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Class naïve patients only	Control group standard of care	Funding	Relevance	Comments
Perlis, 2006	No	NA	Lilly	Yes; can only be generalized to patients without psychotic features.	
Potkin, 2005	NR	No (PCT)	Pfizer	Yes	
Sachs, 2004	Unclear	Yes	AstraZeneca	Yes	
Sachs, 2005	No	Yes	Bristol-Myers Squibb and Otsuka Pharmaceuticals? Funder not clearly stated	Yes	

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, 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
Thase, 2008	Yes	NR	Yes	Yes	Yes	Yes	Yes
Tohen, 2002	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	Post-randomization exclusions	Quality rating
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	Yes, small #, described in Figure 1	Fair
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%)	No	Fair
Tohen, 2002	Yes, No, No, No	No/No	334/344	No	Good

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

External Validity

Author, year	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ washout
Thase, 2006	799/509/506	Diagnosis of an Axis I disorder other than bipoloar disorder that was the primary focus of treatment within 6 months before screening, current episode of depression more than 12 months or less than 4 weeks in duration, a history of nonresponse to an adequate (6 weeks) trial of more than 2 classes of anti-depressants during the current episode, a diagnosis of substance dependence (DSM-IV), or substance use (except nicotine) within 12 months of screening, a clinical significant medical illness, or current serious suicidal or homicidal risk.	Yes/Yes
Thase, 2008	NR/NR/Study 1=374, Study 2=375	Primary psychiatric disorder other than bipolar I disorder with a major depressive episode; late-onset depression (beyond age 55 years); experiencing their first depressive episode; who experienced ≥ 6 manic and/or major depressive episodes within 12 months before randomization; cognitive disorder; psychotic disorder; borderline or antisocial personality disorder; meeting DSM-IV-TR criteria for substance abuse (or dependence) within the past 3 (or 6) months; diagnosis or treatment of obsessive compulsive disorder, bulimia nervosa or attention deficit hyperactivity disorder within the previous 3 months; failed 2 adequate trials of 2 different classes of antidepressant treatment in combination with lithium, valproic acide, carbamazepine, or oxcarbazepine within the current episode; considered to be a significant risk of suicide	No/No
Tohen, 2002	504/NR/344	None	Run-in of 2 weeks on lithium or valproate, wash-out of 1 week of all other concomitant medications

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Class naïve patients only	Control group standard of care	Funding	Relevance	Comments
Thase, 2006	No	Yes	AstraZeneca	Yes	
Thase, 2008	No	Yes	Bristol-Myers Squibb and Otsuka Pharmaceutical Co, Ltd.	Yes	
Tohen, 2002	No	Yes	Lilly Research Laboratories	Yes	

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	NR	Yes	Yes	Yes	Yes	Yes
Tohen, 2003 "a 12 week double-blind"	NR	Yes	Yes	Yes	Yes	Yes	Yes
Tohen, 2005	Open-label phase: yes Double-blind taper phase: unclear ("a priori determined" but exact method not explained)	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
Tohen, 1999	NR	NR	NR	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	Post-randomization exclusions	Quality rating
Tohen, 2003	Yes, No, No, No	No/No	248/251 (99%) included	No	Good
Tohen, 2003 "a 12 week double-blind"	Yes, No, No, No	No/No	Yes	No	Good
Tohen, 2005	Yes NR Yes NR	Yes (0.9% olanzapine group, 0.5% lithium group)/ No	Yes for both open-label and double-blind phase	No	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	NR	Fair
Tohen, 1999	Yes NR NR NR	NR NR	No, 3 (2.2%) patients excluded due to not having a post-baseline assessment	No	Fair

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

External Validity

Author, year	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ washout
Tohen, 2003	NR/NR/251	Any of the following was considered grounds for exclusion: serious and unstable medical illness; DSM-IV substance dependence within the last 30 days (except nicotine or caffeine); documented history of intolerance to olanzapine or divalproex; treatment with lithium, an anticonvulsant, or an antipsychotic medication within 24 hours of randomization; treatment with clozapine within 4 weeks of randomization; and serious suicidal risk.	No run-in Wash-out: Lithium/anticonvulsants/antipsychotics = 24hrs Clozapine = 4 weeks
Tohen, 2003 "a 12 week double-blind"	498/NR/453	If they had a serious, unstable medical illness, had DSM-IV substance dependence (except nicotine or caffeine) within the past 30 days; or were considered a serious risk of suicide.	No run-in Wash-out: psychotriopic medications = 1 day
Tohen, 2005	NR/NR/543	Serious, unstable medical illness; DSM-IV substance dependence criteria within the past 30 days; treatment with a depot neuroleptic within 6 wks of randomization; considered to be a serious suicide risk; history of intolerance or lack of previous response to an adequate trial of lithium or olanzapine	NR/NR
Tohen, 2006	910/731/361	Open-label phase: Unable to tolerate minimum dose of olanzapine Double-blind phase: NR	2-7 day screening followed by randomization at 6-12 wks/washout NR
Tohen, 1999	NR/NR/139	Serious, unstable illness such that hospitalization was anticipated within 3 months or death was anticipated within 3 years; DSM-IV-defined substance dependence (except nicotine or caffeine) within the past 3 months; and serious risk of suicide	No/No

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Class naïve patients only	Control group standard of care	Funding	Relevance	Comments
Tohen, 2003	No	Yes	Lilly Research Laboratories	Yes	
Tohen, 2003 "a 12 week double-blind"	No	Yes	Lilly Research Laboratories	Yes	
Tohen, 2005	No	Yes	Lilly Research Laboratories	Yes Note: double-blind study phase participants limited to responders from open-label phase	
Tohen, 2006	No	Yes	Lilly Research Laboratories	Yes Note: double-blind study phase participants limited to responders from open-label phase	
Tohen, 1999	No	Yes	Eli Lilly and Co	Yes	

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, 2000	Yes	No; personnel at the site assigned a patient to the next available kit	Yes	Yes	Yes	Yes	Yes
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
Vieta, 2005	Unclear - "fixed randomization schedule" but method not explained	NR	Yes	Yes	NR	Yes	Yes
Yatham, 2007	NR; larger portion received Li vs DVP - investigators were asked to chose 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	Post-randomization exclusions	Quality rating
Tohen, 2000	Yes NR NR NR	No No	No, 5 (4.3%) patients excluded due to not having a post-baseline assessment	No	Fair
Tohen, 2003	Yes NR NR NR	No No	No	No	Fair
Tohen, 2004	Yes NR NR NR	NR NR	Yes	No	Fair
Vieta, 2005	Yes NR NR NR	Yes (3 aripiprazole group, 4 haloperidol group)/No	Yes - separate ITT analyses for efficacy and safety	NR	Fair
Yatham, 2007	Yes NR NR NR	Yes reported; overall discontinuation rates: 39.8% placebo vs. 33% quetiapine group (significance not reported).	Yes	NR	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

External Validity

Author, year	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ washout
Tohen, 2000	NR/NR/115	Serious, unstable medical illness; DSM-IV substance dependence (except nicotine or caffeine) within the past 3 months; and serious suicidal risk	No No
Tohen, 2003	NR/1072/833	History of alcohol or substance dependence within the previous 3 months, suicidal behavior within the previous 3 months, or an unstable or untreated medical disorder; score of 15 or greater on the YMRS during weeks 1 to 3 of treatment	No/Yes
Tohen, 2004	NR/160/99	Pregnancy, serious and unstable medical illness; DSM-IV substance dependence within the past 30 days; documented history of intolerance to olanzapine; and serious suicidal risk	No/No
Vieta, 2005	NR/372/347	Rapid cycling bipolar 1 disorder; durations of current manic episode of more than 4 wks; proven substance misuse; patient considered unresponsive to antipsychotics; patient at significant risk of suicide; recent treatment with long-acting antipsychotic, lithium or divalproate; use of psychotropic medications other than benzodiazapines within 1 day of randomization; fluoxetine treatment in the past 4 wks; previous enrollment in an aripiprazole clinical study.	NR/1-3day washout
Yatham, 2007	250/211/209	Stated as being the same as those used in the previously reported study (Sachs et al 2004 Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disord 6: 213-223).	Yes/NA

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Class naïve patients only	Control group standard of care	Funding	Relevance	Comments
Tohen, 2000	No	Yes	Lilly Research Laboratories	Yes	
Tohen, 2003	No	Yes	Lilly Research Laboratories	Yes	
Tohen, 2004	No	Yes	Lilly Research Laboratories	Yes	
Vieta, 2005	NR	Yes	Bristol-Myers Squibb and Otsuka Pharmaceuticals	Yes	
Yatham, 2007	No	Yes	Yes	Yes	

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?
Yatham, 2003 International	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	Post-randomization exclusions	Quality rating
Yatham, 2003	Yes	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	8(5.3%) patients excluded from efficacy analysis due to having < 2 assessments	Fair
International	NR	No			
	NR				
	NR				

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

External Validity

Author, year	Number screened/eligible/enrolled	Exclusion criteria	Run-in/ washout
Yatham, 2003 International	NR/157/151	Another DSM-IV Axis I diagnosis other than nicotine or caffeine dependence; seizure disorder requiring medication; history of alcohol or drug misuse or dependence within the 3 months prior to the study; people at imminent risk of causing injury to themselves or others or of causing property damage; serious or unstable medical disease; clinically significant laboratory abnormalities; severe drug allergy or hypersensitivity; history of neuroleptic malignant syndrome	No/Yes

Evidence Table 9. Quality assessment of randomized controlled trials of patients with bipolar disorder

Author, year	Class naïve patients only	Control group standard of care	Funding	Relevance	Comments
Yatham, 2003 International	No	Yes	Janssen Pharmaceutica Products, LP	Yes	

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	Population	Age Gender Ethnicity
Comparative Studies							
Hassan, 2007 USA	Medicaid administrative claims database	Retrospective	January 1, 1999, to December 31, 2001	2 years	Risperidone, olanzapine, quetiapine, or typical antipsychotic	Under 65 years medicaid recipients	NR NR NR
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	Bipolar and manic disorders	Mean age=36 years 50% male Ethnicity NR

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Comparative Studies			
Hassan, 2007 USA	NR/832/825	NA/NA/825	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 Persistance - total days from the index prescription fill date until the occurrence of a filled prescription for any other index or nonindex ntipsychotic 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.
Gianfrancesco, 2007 United States	NR/NR/10,037	NA/NA/10,037	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)

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Safety Outcomes	Comments
Comparative Studies		
Hassan, 2007 USA	NR	
Gianfrancesco, 2007 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	Population	Age Gender Ethnicity
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	Bipolar disorder	Mean age 37 years 32% male Ethnicity NR
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	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

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Zhu, 2007 United States	NR NR 1516	NA NA 1516	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	NR/NR/920 cases and 5258 controls	NR/NR/920 cases and 5258 controls	Of the 920 cases, 41% received atypical antipsychotics: 20% olzanzapine; 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
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	Population	Age Gender Ethnicity
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	Refractory bipolar disorder	Mean age: 38.6 years 53% male Ethnicity NR
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	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)

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Noncomparative Studies			
Clozapine			
Zarate, 1995 United States	193 17 17	0 0 17	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	NR	NR	symptomatic remission of mania during 1 year: 79 (69.9%)
Hennen, 2004 United States	NR 139	NR 113	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 (ie, 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	Population	Age Gender Ethnicity
Dennehy, 2003 United States	NR	Prospective	1998-1999	8 weeks	Olanzapine 5-12 mg	Bipolar I disorder	Mean age: 39 years 26.7% male Ethnicity NR
Gonzalez-Pinto, 2001 Spain	Santiago Hospital Psychiatric Unit	Prospective	March 1999 - February 1998	NR	Olanzapine 5-20 mg other antipsychotics (haloperidol and levomepromazine)	Mania	Mean age: 37.1 years 53.4% male Ethnicity NR

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Dennehy, 2003 United States	NR NR 15	5 3 15	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	86 44 44	0 0 44	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% oedema 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	Population	Age Gender Ethnicity
Janenawasin, 2002 United States	NR	Prospective	NR	9 weeks	Olanzapine 7.8 mg	Bipolar I, bipolar II or bipolar not otherwise specified	Mean age: 37.7 years 48% male Ethnicity NR
McElroy, 1998 United States	NR	Prospective	NR	101.4 days	Olanzapine 14.1 mg	Bipolar I disorder	NR
Vieta, 2001 Spain	Naturalistic: Clinic nr	Prospective	NR	303 days	Olanzapine 8.2 mg	Treatment resistant bipolar disorder	Mean age: 39.9 56.5% male Ethnicity NR

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Janenawasin, 2002 United States	NR NR 25	NR NR 25	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
McElroy, 1998 United States	NR NR 14	NR NR 14	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
Vieta, 2001 Spain	NR NR 23	6 (23%) withdrawn 1 (4.3%) lost to fu 23 analyzed	NR

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	
Vieta, 2001 Spain	Weight gain 3 (13%) Hospitalizations 3 (13%)	

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	Population	Age Gender Ethnicity
Risperidone							
Bahk, 2004 Korea	81 nationwide sites in Korea	Prospective	August 2002 - December 2002	6 weeks	Risperidone 3.1 mg	bipolar manic or hypomanic episode	Mean age: 37.9 years 45.8% male 100% Asian
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	Bipolar manic 78.9% Bipolar mixed 21.1%	Mean age: 41.3 years 45.9% male Ethnicity: NR

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Risperidone			
Bahk, 2004 Korea	NR NR 909	18 25 866	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
Bowden, 2004 United States	NR 156 85	35 4 48	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
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	
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	Population	Age Gender Ethnicity
Vieta, 2002 Spain	NR	Prospective	NR	6 weeks	Risperidone 4.9 mg	bipolar I or II disorder	Mean age: 40.7 years 40.2% male Ethnicity NR

Evidence Table 10. Observational studies in patients with bipolar disorder

Author, year Country	Exposed Eligible Selected	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Vieta, 2002 Spain	NR NR 174	12 3 159	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?	Adequate sample size?
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	Yes; N=10,037
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	Yes (cases 920, controls 5258)
Hassan, 2007	Yes	Yes	Yes	NA	Yes	Yes	Yes	12 months	Unclear - 825
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	Unclear - 1516
Vieta, 2001	Yes	Yes	No, definition of "weight gain" was not specified	No	No	No	NR	Yes	No, 23

Evidence Table 11. Quality assessment of observational studies in patients with bipolar disorder

Author, year	Overall adverse event assessment quality	Comments
Gianfrancesco, 2007	Fair	
Guo, 2006	Fair	case control study
Hassan, 2007	Fair	
Zhu 2007	Fair	
Vieta, 2001	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	Additional study eligibility criteria
Ballard, 2006 (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;	Use of a validated and published method for evaluating aggression. Excluded patients receiving other psychotropic drugs during the study
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.	All studies were conducted by Eli Lilly

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Main efficacy results	Adverse events
Ballard, 2006 (Cochrane Review)	**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	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	Aims	Literature search dates	Population included	Drugs included	Study designs included	Additional study eligibility criteria
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-controled, parallel group trials.	Numbers of patients randomized, dropouts, and deaths were obtainable.
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.	Numbers of patients randomized and at least one outcome measure or adverse event was obtainable; unpublished studies included.

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Main efficacy results	Adverse events
Schneider, 2005	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)
Schneider, 2006	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)

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	Additional study eligibility criteria
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	Outcomes for neuropsychiatric symptoms (e.g., hallucinations, delusions, combativeness, verbal aggression, psychomotor agitation, wandering)
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	Effect on BPSD or adverse events as a primary outcome; Intention-to-treat analysis used

Evidence Table 12. Systematic reviews of atypical antipsychotics in patients with behavioral and psychological symptoms of dementia

Author Year	Main efficacy results	Adverse events
Sink, 2005	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.
van Lersel, 2005	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 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
Schneider, 2001 Schneider, 2006 Ismail, 2007 US CATIE Trial (Phase 1) (FAIR)	421	Up to 36 weeks	Double-blind, multicenter, placebo-controlled Outpatients or assisted living facilities
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.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Eligibility criteria
Schneider, 2001 Schneider, 2006 Ismail, 2007 US CATIE Trial (Phase 1) (FAIR)	Dementia of the Alzheimer's type or probable Alzheimer's disease ; MMSE score between 5 and 26 ; ambulatory, living at hom eor in an assisted-living facility. Delusions, hallucinations, aggression, or agitation that developed afte the onset of dementia and was severe enough to disrupt their functioning and justify treatment with antipsychotic drugs. Signs and symptoms of psychotis, 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 ewwre randomized, a severity rating ofat least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behaviour on the BPRS. Alternatively, a frequency rating of "often" or "more frequently" and a severity rating ofat 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 ws required to participate in the assessments.
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	Age 40 or older. All patients exhibited clinically significant psychotic symptoms associated with Alzheimer's desease, 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 Delusons items on the NPI or NPI-NH.

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)
Schneider, 2001 Schneider, 2006 Ismail, 2007 US CATIE Trial (Phase 1) (FAIR)	Diagnosis of a primary psychotic disorder, delirium, other demential such as vascular dementia or Lewy-body dementia, or psychosis, agitation, or aggression that could be better accounted for by another medical condition, medicaiton, or substance abuse. If they required psychiatric admission, were suicidal, were going to receive treatment with a cholinesterase inhibitor or antidepresant medicaiotn, 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
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

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Run-in/washout Period	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Schneider, 2001 Schneider, 2006 Ismail, 2007 US CATIE Trial (Phase 1) (FAIR)	Not reported	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
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	Atypical antipsychotic use was disallowed within 30 days, lithium or anticonvulsant use within 2 weeks before the placebo/wahsout period. Oral conventional antipsychotic use was allowed up to 3 days before randomization. 3 to 14-day placebo washout period.	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

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures
Schneider, 2001 Schneider, 2006 Ismail, 2007 US CATIE Trial (Phase 1) (FAIR)	521/471/421	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
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	Number screened, eligible not reported/494 enrolled	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.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Method of outcome assessment and timing of assessment	Results
Schneider, 2001 Schneider, 2006 Ismail, 2007 US CATIE Trial (Phase 1) (FAIR)	Not described	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% olanazapine 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
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	Patients were assessed weekly for the first 2 weeks of the study and biweekly thereafter	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

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Method of Adverse Event Assessment	Adverse events
Schneider, 2001 Schneider, 2006 Ismail, 2007 US CATIE Trial (Phase 1) (FAIR)	Assessed by eliciting information about the occurrence of AEs. Weight, prolactin, glucose, cholesterol, and triglyceride levels were measured at weeks 12, 24, and 36.	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
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	Safety assessed from spontaneous reports of treatment-emergent adverse events, usign the Coding Symbols for a Thesaurus of Adverse Reaction Tems (CoSTART) dictionary, and from vital signs, ECG, analysis of laboratory tests and MMSE changes. Motor symptoms were meausured with the Simpson-Angus Scale, the Barnes Akathisia Scale, and the AIMS	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.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Total withdrawals/ Withdrawals due to AEs
Schneider, 2001 Schneider, 2006 Ismail, 2007 US CATIE Trial (Phase 1) (FAIR)	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%
Deberdt, 2005 US (FAIR) Eli Lilly Clinical Study Summary F1D-MC-HGGU	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)

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
Ellingrod., 2002 US (POOR)	19	8 weeks	Single-blind, nonrandomized. Four rural nursing care facilities in one city.
Fontaine, 2003 US (POOR)	39	2 weeks	Double-blind, long-term care facilities.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Eligibility criteria
Ellingrod., 2002 US (POOR)	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)	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)
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.
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

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Run-in/washout Period	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Ellingrod., 2002 US (POOR)	None	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)
Fontaine, 2003 US (POOR)	3-day washout of psychotropic drugs.	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)

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures
Ellingrod., 2002 US (POOR)	Number screened, eligible not reported/19 enrolled	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
Fontaine, 2003 US (POOR)	Number screened not reported/47 "recruited"/39 enrolled	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

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Method of outcome assessment and timing of assessment	Results
Ellingrod., 2002 US (POOR)	Assessment at baseline, 1 month, and 2 months by one rater.	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)
Fontaine, 2003 US (POOR)	Assessment at baseline, observation on days 1,2,3,5,8,10,12, and 15 by study nurse and study physician.	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)

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Method of Adverse Event Assessment	Adverse events
Ellingrod., 2002 US (POOR)	AIMS, Simpson-Angus Extrapyramidal Symptoms Scale, Barnes Akathasia Scale	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)
Fontaine, 2003 US (POOR)	AIMS, Simpson-Angus Extrapyramidal Symptoms Scale, Barnes Akathasia Scale	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 Akathasia 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)

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Total withdrawals/ Withdrawals due to AEs
Ellingrod., 2002 US (POOR)	Overall: 31.1% risperidone, 37.7% olanzapine, 20.2% placebo Due to adverse events: NR
Fontaine, 2003 US (POOR)	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
Gareri, 2004 Italy (POOR)	60	8 weeks	Double-blind, setting not reported
Mulsant, 2004 US (POOR)	86	6 weeks	Double-blind, multicenter, long-term care facilities

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Eligibility criteria
Gareri, 2004 Italy (POOR)	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)	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)
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.
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 definnite diagnosis of psychotis 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.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Run-in/washout Period	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Gareri, 2004 Italy (POOR)	10-day washout	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
Mulsant, 2004 US (POOR)	3-day washout, 7-day single-blind placebo run-in.	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)

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures
Gareri, 2004 Italy (POOR)	NR/NR/60	NR/NR/60	Primary outcome measure: NPI
Mulsant, 2004 US (POOR)	NR/NR/86	17/NR/85	Primary outcome measures: Udvalg for Kliniske Undersogelser (UKU) ratiing scale measuring peripheral anticholinergic effects, or a site report of a somnolence adverse event. Efficacy outcomes: NPI; abbreviated cognitive assessment.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Method of outcome assessment and timing of assessment	Results
Gareri, 2004 Italy (POOR)	Assessment at baseline, 4 and 8 weeks.	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 respone 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)
Mulsant, 2004 US (POOR)	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).	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).

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Method of Adverse Event Assessment	Adverse events
Gareri, 2004 Italy (POOR)	Hoehn and Yahr Scale used for evaluating parkinsonism, administered at baseline, 4 weeks, and 8 weeks.	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%).
Mulsant, 2004 US (POOR)	Udvalg for Kliniske Undersogelser (UKU) rating scalse measuring peripheral anticholinergic effects (including visual accomodation disturbances, dry mouth, constipation, micturition disturbances, and palpitations) or a site report of a somnolence adverse event. ESRS	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.

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Total withdrawals/ Withdrawals due to AEs
Gareri, 2004 Italy (POOR)	Not reported
Mulsant, 2004 US (POOR)	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
Rainier, 2007 Austria (FAIR)	72	8 weeks	Multicenter Outpatients

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Eligibility criteria
Rainier, 2007 Austria (FAIR)	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 adn aberrant motor behavior, and an MMSE total scoe 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.

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)
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 thecountry-specific Prescribing Information; history of nonadherence, use of other antipsychotics; medical hisory 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 fo rtheir 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)

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Run-in/washout Period	Allowed other medications/interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Rainier, 2007 Austria (FAIR)	Not reported	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-termporal lobe dementia syndrome, Lewy body dementia)

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures
Rainier, 2007 Austria (FAIR)	NR/NR/72	6/1/1965	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

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Method of outcome assessment and timing of assessment	Results
Rainier, 2007 Austria (FAIR)	Baseline, week 4, week 8	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%

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Method of Adverse Event Assessment	Adverse events
Rainier, 2007 Austria (FAIR)	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	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

Evidence Table 13. Head-to-head trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial name (Quality Score)	Total withdrawals/ Withdrawals due to AEs
Rainier, 2007 Austria (FAIR)	10.5% quetiapine, 8.8% risperidone/ 5.3% quetiapine, 2.9% risperidone

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
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 US	Method not described	Not reported	MMSE score (olanzapine 13.7, risperidone 14.7, placebo 15.4) signficantly 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 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

	External Validity			
Author, year **Country**	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**	**Class naïve patients only?**
Ballard, 2005 UK Quetiapine and rivastigmine Fair	282/150/93 82 completed	We excluded 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.	Run-in; yes Washout; yes No use of medications for 4 weeks prior to study	No
Deberdt, 2005 US	NR/NR/494	Parkinson's disease, Lewy-body dementia, Pick's disease, frontotemporal dementia; or a MMSE score <5 or >24.	3- to 14-day placebo washout	NR
Ellingrod, 2002 US	Number screened, eligible not reported/19 enrolled	Intracranial lesion or a history of severe head trauma.	None	No
Fontaine, 2003 US	Number screened not reported/47 "recruited"/39 enrolled	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.	3-day washout of psychotropic drugs.	No

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Control group standard of care?	Funding	Comments
Ballard, 2005 UK Quetiapine and rivastigmine Fair	Yes	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 US	Yes	Eli Lilly	
Ellingrod, 2002 US	Yes	Supported by the 1999 American College of Clinical Pharmacy Research Award.	
Fontaine, 2003 US	Yes	Supported by Eli Lilly and Company.	

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
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)
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 institutionalizaton (11.9 vs 27.1 months)	Yes	Not reported (describd as double blind)	Not reported (describd as double blind)	Not reported (describd as double blind)
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

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
Gareri, 2004 Italy	NR	NR	Yes	No	Poor
Mulsant, 2004 US	Attrition yes (but not reported by group), others no.	Unable to determine	No (excluded 1 olanzapone patient with no postbaseline data)	No	Poor
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

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity			
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**	**Class naïve patients only?**
Gareri, 2004 Italy	NR/NR/60	NR	10-day washout (drugs not specified)	NR
Mulsant, 2004 US	NR/NR/86	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 definnite diagnosis of psychotis prior to the onset of dementia, and an inability to otherwise cooperate with the study procedures.	3-day washout	NR
Chan, 2001 Hong Kong	Number screened, eligible not reported, 58 enrolled	Presumptive diagnosis of Lewy Body Dementia, other neurological or medical conditions which diminished cognitive function (e.g., hypothyroidism), other psychiatric disorders which might contribute to the psychotic symptoms (e.g., schizophrenia, delusional disorder), unstable medical conditions (e.g., poorly controlled hypertension, angina or diabetes), clinically relevant abnormal ECGs or laboratory tests, a history of allergic reaction to antipsychotic treatment or a history of Neuroleptic Malignant Syndrome.	7- to 14-day washout during which all psychotropic and antiparkinsonian drugs were stopped.	No
De Deyn, 1999 Multiple European countries.	Number screened not reported/371 eligible/344 enrolled (27 dropped out during washout)	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.	1-week single-blind washout phase during which all psychotropic medications were discontinued.	No

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Control group standard of care?	Funding	Comments
Gareri, 2004 Italy	NR	Ministry of Health	
Mulsant, 2004 US	Yes	Janssen	
Chan, 2001 Hong Kong	Yes	Sponsored by Janssen Research Foundation	
De Deyn, 1999 Multiple European countries.	Yes	Supported in part by a grant from the Janssen Research Foundation.	

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
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)
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

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
Meehan, 2002 US, Russia, and Romania	Attrition yes, others no.	No	Yes	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

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity			
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**	**Class naïve patients only?**
Meehan, 2002 US, Russia, and Romania	331/NR/272	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 injetable 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.	None	NR
Suh, 2004 South Korea	280 screened/#eligible not reported/120 enrolled.	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 controled 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.	1-week washout period during which all psychotropic medications were discontinued.	No
Tariot, 2004 (poster) US	# screened, eligible not reported/284 enrolled	Not reported	No placebo run-in; antipsychotics discontinued >48 hours	Not reported

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Control group standard of care?	Funding	Comments
Meehan, 2002 US, Russia, and Romania	Yes	Eli Lilly	
Suh, 2004 South Korea	Yes	Financially supported by Janssen Korea, Seoul, Korea.	
Tariot, 2004 (poster) US	Unable to determine	Not reported; one author from AstraZeneca	

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
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
De Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa	Method not reported	Not reported	Yes	Yes	Yes	Not reported	Yes
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

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
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
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
Katz, 1999 US	Attrition yes, others no.	No	No: results on 617/625 at endpoint, 435/625 at week 12.	No	Fair

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity			
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**	**Class naïve patients only?**
Brodaty, 2003 Frank, 2004 Australia, New Zealand	Number screened not reported/384 eligible/345 enrolled	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.	Maximum 7-day single-blind placebo washout period during which existing psychotropic medication was discontinued.	No
De Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa	Number screened, eligible not reported/652 enrolled	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.	Placebo run-in for up to maximum 14 days.	No
Katz, 1999 US	729 screened/625 eligible/625 enrolled	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.	Single-blind placebo washout of 3 to 7 days.	No

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Control group standard of care?	Funding	Comments
Brodaty, 2003 Frank, 2004 Australia, New Zealand	Yes	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.	
De Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa	Yes	Sponsored by Eli Lilly and Company; corresponding author employed by Lilly Research Laboratories.	
Katz, 1999 US	Yes	Supported by a grant from the Janssen Research Foundation.	

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
Kennedy, 2005 US Olanzapine Fair	Unclear; states 2:1 ratio	Unclear	Yes	Yes	NR	NR	NR
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

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
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
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

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity			
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**	**Class naïve patients only?**
Kennedy, 2005 US Olanzapine Fair	446/368/268	Exclusion criteria included having a score >1 on any one of the following Neuropsychiatric Inventory (NPI, Cummings et al., 1994) items: delusions, hallucinations, agitation/ aggression, dysphoria; having a score of 1 on any three of these four items; current use of any cholinesterase inhibitor, antioxidant or herbal supplements considered to have possible beneficial effects in improving cognitive features of Alzheimer's within 4 weeks prior to enrollment into the study; a history of any other DSM-IV Axis I disorder, or any neurological condition other than Alzheimer's dementia. In general, concomitant medications with primarily central nervous system activity, including antidepressants, were disallowed.	Yes/Yes 10-18 day washout	No
Mintzer, 2006 US	560/87/473	Patients excluded had recently been treated with neuroleptic injections, had other medical conditions that diminish cognition, or had other psychiatric disorders that produce psychotic sympotms. Patients with epilepsy, recent diagnoses or cancer (except nonmelanoma skin cancers), unstable medical conditios, changes in prescription medications 30 days before screening, or significant baseline laboratory or ECG abnormalities wer also excluded. Patients were withdrawn if their behavior worsened considerably, they withdrew consent, or their randomizaton code was broken.	One week placebo washout. Period reduced for patients not using psychotropic medications and for patietns whose psycohosis or agitation worsened.	NR

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Control group standard of care?	Funding	Comments
Kennedy, 2005 US Olanzapine Fair	Yes	Eli Lilly	
Mintzer, 2006 US	Yes	Johnson & Johnson	

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
Rainer, 2007 Austria quetiapine versus risperidone Fair	Unclear; states computer generated scheme	Only assessors blinded	Yes	Yes	Yes	No	No
Savaskan, 2006 open-label comparative study haloperidol vs. quetiapine Fair-Poor	Unclear	Unclear	Yes; only sex and age provided	Yes	unclear	unclear	No

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
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
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

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity			
Author, year **Country**	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**	**Class naïve patients only?**
Rainer, 2007 Austria quetiapine versus risperidone Fair	NR/NR/72	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 (except prothipendyl 80 mg/day and dixyrazin 25 mg/day) or tranquilisers (except zolpidem [10 mg/day], triazolam [0.25 mg/day] and oxazepam [15e50 mg/day]); having a medical history of advanced, severe or unstable disease of any type that could interfere with study; having a current diagnosis of uncontrolled seizure disorder, active peptic ulceration, severe or unstable cardiovascular disease, or of acute or severe asthmatic conditions; clinically significant abnormalities on any of the following evaluations: cardiovascular, vital signs for their age, physical examination, electrocardiogram (ECG); having an authorised representative appointed by the responsible public authority. Also, 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.	Run-in; no Washout; no	No
Savaskan, 2006 open-label comparative study haloperidol vs. quetiapine Fair-Poor	NR/NR/30	The exclusion criteria included known sensitivity to study drugs, evidence of chronic and/or severe renal, hepatic, cardiovascular, pulmonary or 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.	Yes/NR	No

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Control group standard of care?	Funding	Comments
Rainer, 2007 Austria quetiapine versus risperidone Fair	NA	AstraZeneca	Small sample; majority of patients received concomitant medication; patients and investigators were aware of randomisation outcome
Savaskan, 2006 open-label comparative study haloperidol vs. quetiapine Fair-Poor	NA	AstraZeneca (Switzerland) & Swiss National Science Foundation Research Professorship	Short study, small sample size

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
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
Street et al., 2000 US	Yes	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
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
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

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity			
Author, year **Country**	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**	**Class naïve patients only?**
Schneider, 2006 US, 45 sites [CATIE-AD] olanzapine, quetiapine, risperidone, placebo Phase I stated as double-blind Fair	521/507/421	Patients were excluded if they had received a diagnosis of a primary psychotic disorder (e.g., schizophrenia), 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. Patients were also excluded 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.	No/No due to acute symptoms p 1536	No
Street et al., 2000 US	# screened not reported/288 eligible/206 enrolled	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.	3- to 14-day single-blind placebo run-in; patients demonstrating a placebo response were not randomized.	No

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Control group standard of care?	Funding	Comments
Schneider, 2006 US, 45 sites [CATIE-AD] olanzapine, quetiapine, risperidone, placebo Phase I stated as double-blind Fair	Yes	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)
Street et al., 2000 US	Yes	Sponsored in part by Eli Lilly and Company; 11 of 13 authors employed by Lilly Research Laboratories; 10 authors are stockholders in Eli Lilly.	

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
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
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
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
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

	External Validity			
Author, year **Country**	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**	**Class naïve patients only?**
Tariot, 2006 US, 47 sites stated as double-blind quetiapine vs. haloperidol vs. placebo Fair	# screened NR 284 eligible & enrolled 63% completed the study	Exclusion criteria included other clinically significant medical conditions, history of drug-induced agranulocytosis, acute orthostasis, clinically significant abnormal electrocardiogram, or concurrent other Axis I DSM-IV diagnosis.	Run-in, NR Washout >48 hours	No
Zhong et al, 2004 (poster) US	# screened, eligible not reported/333 enrolled	Not reported	Not reported	Not reported
Zhong, 2007 US, 53 centers quetiapine vs. placebo Fair	435/354/333	Exclusion criteria included a 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, cerebrovacular disorders, and abnormal ECG results). Psychotropic medications with few exceptions.	Run-in, Yes Washout, NR	No

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Control group standard of care?	Funding	Comments
Tariot, 2006 US, 47 sites stated as double-blind quetiapine vs. haloperidol vs. placebo Fair	Yes	AstraZeneca Pharmaceuticals LP	23-35% in each group were taking concomitant anxiolytic or hypnotic medications during study
Zhong et al, 2004 (poster) US	Unable to determine	Supported by AstraZeneca	
Zhong, 2007 US, 53 centers quetiapine vs. placebo Fair	Yes	AstraZeneca Pharmaceuticals	High number of participants on concomitant medications; short follow-up

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
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)

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
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 assesments. 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

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity			
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**	**Class naïve patients only?**
Verhey, 2006 Netherlands, 6 sites Olanzapine vs. Haloperidol	NR/NR/59	Clinical diagnosis of delirium, behavioral problems related to infections, metabolic disturbances, med-induced ETOH withdrawal, hypertension, nutritional deficices, any other neurological considtions (including Parkinson's disease, Lewy body disease, etc) that could contribute to psychosis or dementia, hx of serious and unstable somatic disorders, treatment with lithium, anticonvulsants, MAOI, psychostimulants.	Run-in: No Washout: 3-days	No

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Control group standard of care?	Funding	Comments
Verhey, 2006 Netherlands, 6 sites Olanzapine vs. Haloperidol	Yes	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

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	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?**
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
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
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

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
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 olanzepine 5mg	Poor (see comments)
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)
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

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

	External Validity			
Author, year **Country**	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**	**Class naïve patients only?**
Meehan, 2002 Multinational, 38 centers in 3 countries Olanzapine IM vs. Lorazepam IM vs. Placebo IM	331/NR/272	Not reported	Not reported	Not reported
Deberdt 2005 Multicenter, 64 centers Olanzapine vs. Risperidone and placebo	540/NR/494	Not reported	No/Yes, 3-14 days	Not reported
Moretti, 2005 Italy	NR/NR/356	Signs of normal pressure hydrocephalus; previous psychiatric illness or central nervous system disorders or alcoholism	1-week washout period for psychotropics	NR

Evidence Table 14. Quality assessment of trials in patients with behavioral and psychological symptoms of dementia

Author, year Country	Control group standard of care?	Funding	Comments
Meehan, 2002 Multinational, 38 centers in 3 countries Olanzapine IM vs. Lorazepam IM vs. Placebo IM	Yes	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
Deberdt 2005 Multicenter, 64 centers Olanzapine vs. Risperidone and placebo	Yes	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
Moretti, 2005 Italy	Yes	NR	

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	Exclusion criteria
Olanzapine vs haloperidol					
Verhey, 2006 Netherlands (FAIR)	58	5 weeks	Open-label, non-randomized controlled trial	60 years or older, diagnosis of dementia according to DSM-IV criteria, level of agitaton that was clinically judged to represent a clinical problem requiring antipsychotic treatment for a behavior disorder, no use of such drugs within 3 days of inclusion and a score of at least 45 on the CMAI. Agitation operationally defined as: inappropriate verbal, vocal or motor activity that is not judged by an outside observer to be an obvious outcome of the needs or confusion of the individual.	Clinical diagnosis of delirium, behavioral problems related to infections, metabolic distgurbances, medicaiton-induced alcohol withdrawal, hypertension and nutritional deficiencies, any other neurological condition (including Parkinson's disease, Lewy body disease, Huntington's disease, multiple sclerosis, seizure disorder, intracranial space-occupying liesion,k hydrocephalus or history of significant head trauma) that could contribute to psychosis or dementia, apparent or history of serious and unstable somatic disorder including hepatic, renal, gastroesophageal, respiratory, cardiovascular, endocrinological, neurological, immunological or hematological disease and treatment with lithium, anticonvulsants, psychostimulants or reversible MAO.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Interventions (drug, dose)	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
Olanzapine vs haloperidol				
Verhey, 2006 Netherlands (FAIR)	Olanzapine 2.5 mg, 5 mg, and 7.5 mg/day Haloperidol 1 mg, 2, or 3 mg/day	3-day washout if used antipsychotics within 3 days of inclusion	Use of antidepressants or benzodiazepines was allowed, provided that the lowest possible dosage was prescribed and the dosage was stable throughout the study.	Mean age 83 56.9% female race/ethinicity not reported

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures
Olanzapine vs haloperidol				
Verhey, 2006 Netherlands (FAIR)	36.2% Alzheimer's disease, 31.0% vacular dementia, 15.5% mixed dementia, 17.2% dementia NOS; 48.3% living in a nursing home	NR/NR/59	10/0/58	CMAI MMSE NPI CGI

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Method of outcome assessment and timing of assessment	Results	Method of adverse event assessment
Olanzapine vs haloperidol			
Verhey, 2006 Netherlands (FAIR)	CMAI and CGI at all visits (week 0, weeks 1, 2, 3, and 5); NPI at visits 1, 3, and 5	Change from baseline to endpoint, olanzapine vs haloperidol CMAI Total: -10.07 vs -16.57 (p=0.338) NPI Total: -11.09 vs -18.87 (p=0.171) NPI Distress: -3.4 vs -5.8 (p=0.305) NPI Psychosis: -1.0 vs -1.4 (p=0.778) NPI Hyperactivity: -6.9 vs -9.9 (p=0.364) NPI Mood: -3.2 vs -2.7 (p=0.823) CGI: -0.7 vs -1.0 (p=0.917)	UKU side-effects rating scale at all visits AIMS and Simpson-Angus Scale at visits 1 and 5

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Adverse events
Olanzapine vs haloperidol	
Verhey, 2006 Netherlands (FAIR)	Change from baseline to endpoint, olanzapine vs haloperidol AIMS: 0 vs 0.42 (p=0.887) SAS: -1.44 vs 1.41 (p=0.120) MMSE: 0.53 vs -0.13 (p=0.481) UKU: -0.7 vs -0.2 (p=0.31)

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	Exclusion criteria
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.	Signs of normal pressure hydrocephalus; previous psychiatric illness or CNS disorders, alcoholism
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.	Known sensitivity to study drugs, evidence of chronica and/or severe renal, hepatic, cardiovascular, pulmonary of gastrointestinal impairment or cancer, other antipsychotic meication than the study drugs, participation in any other drug trial and contraindications as detailed inthe country-specific prescribing information for the study drugs.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Interventions (drug, dose)	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
Moretti, 2005 (FAIR)	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	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
Quetiapine vs haloperidol				
Savaskan, 2006 Switzerland (POOR)	Quetiapine mean dose 125 mg Haloperidol mean dose 1.9 mg	Maximum 7-day run-in period (not described)	Concomitant medication was continued and documented. All patients received a cholinesterase inhibitor (galantamne 2 X 8 mg)	Mean age 82 68.2% female Race/ethnicity not reported

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures
Moretti, 2005 (FAIR)	Subcortical vascular dementia: 11.6% Multi-infarct dementia: 88.4%	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
Quetiapine vs haloperidol				
Savaskan, 2006 Switzerland (POOR)	All had Alzheimer's Disease, no prior history of psychiatric diagnosis	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)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Method of outcome assessment and timing of assessment	Results	Method of adverse event assessment
Moretti, 2005 (FAIR)	Hachinski Ischemic score and Matthew's Stroke Scale at first and last visit, others at every visit	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 equlilbrium: -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
Quetiapine vs haloperidol			
Savaskan, 2006 Switzerland (POOR)	Baseline during run-in, 1 day prior to commencing study drugs, and end of week 5	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

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Adverse events
Moretti, 2005 (FAIR)	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)	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

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	Exclusion criteria
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.	Other clinically significant medical conditions, history of drug-induced agranulocytosis, acute orthostasis, clinically significant abnormal electrocardiogram, or concurrent other Axis I DSM-IV diagnosis.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Interventions (drug, dose)	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
Tariot, 2006: full publication (Replaces Tariot 2004, previously available as a poster only) (FAIR)	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.	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.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures
Tariot, 2006: full publication (Replaces Tariot 2004, previously available as a poster only) (FAIR)	100% Alzheimer's dementia	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)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Method of outcome assessment and timing of assessment	Results	Method of adverse event assessment
Tariot, 2006: full publication (Replaces Tariot 2004, previously available as a poster only) (FAIR)	Screening, baseline, weeks 2, 4, 6, and 10	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.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Adverse events
Tariot, 2006: full publication (Replaces Tariot 2004, previously available as a poster only) (FAIR)	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	Exclusion criteria
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).	No additional

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Interventions (drug, dose)	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
Risperidone vs haloperidol				
Chan et al, 2001 Hong Kong (FAIR)	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.	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

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures
Risperidone vs haloperidol				
Chan et al, 2001 Hong Kong (FAIR)	79% Alzheimer's dementia, 21% vascular dementia	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).

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Method of outcome assessment and timing of assessment	Results	Method of adverse event assessment
Risperidone vs haloperidol			
Chan et al, 2001 Hong Kong (FAIR)	Baseline, weeks 4, 8, and 12. Additional CMAI ratings at weeks 2, 6, and 10.	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 Akathasia Scale

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Adverse events
Risperidone vs haloperidol	
Chan et al, 2001 Hong Kong (FAIR)	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	Exclusion 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.	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.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Interventions (drug, dose)	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	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.	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, <1% Asian

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	74% Alzheimer's dementia, 33% Vascular Dementia (7% had both diagnoses)	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)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Method of outcome assessment and timing of assessment	Results	Method of adverse event assessment
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	Evaluations at selection, baseline, weeks 1, 2, 4, 6, 8, 10, 12.	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

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Adverse events
De Deyn et al, 1999 Multiple European countries (FAIR) Engelborghs (subanalysis)	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	Exclusion 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.	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 controled 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.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Interventions (drug, dose)	Run-in/washout period	Allowed other medications/interventions	Age Gender Ethnicity
Suh et al, 2004 South Korea (FAIR) Suh 2006 [post hoc analyses]	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.	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)

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures
Suh et al, 2004 South Korea (FAIR)	65.8% Alzheimer's dementia 28.3% vascular dementia 5.8% mixed	280 screened/# eligible not reported/120 enrolled	6 withdrawn/0 lost to followup/114 analyzed	BEHAVE-AD-K, CMAI-K, AND CGI-C

Suh 2006 [post hoc analyses]

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Method of outcome assessment and timing of assessment	Results	Method of adverse event assessment
Suh et al, 2004 South Korea (FAIR) Suh 2006 [post hoc analyses]	Patients assessed weekly during the first 4 weeks and then every 2 weeks (twice) until the end of the final (8th week)	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=0.00 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.

Evidence Table 15. Active-control trials in patients with behavioral and psychological symptoms of dementia

Author, year (Quality score)	Adverse events
Suh et al, 2004 South Korea (FAIR)	Withdrawals due to Aes: 7% risperidone 3% haloperidol
Suh 2006 [post hoc analyses]	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 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria	Exclusion 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.	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.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Olanzapine (oral)					
Street, 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	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.	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

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

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
Olanzapine (oral)				
Street, 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	# screened not reported/288 eligible/206 enrolled	54 withdrawn/5 lost to followup/200 analyzed	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.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Method of adverse event assessment
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	Simpson-Angus Scale, Barnes Akathisia Scale, AIMS

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Adverse events
Olanzapine (oral)	
Street, 2000 US (GOOD) Kennedy, 2001 (subanalysis) Street 2001 (one-year followup)	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

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria	Exclusion criteria
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.	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.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	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.	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)

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

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
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	Number screened, eligible not reported/652 enrolled	184 withdrawn/lost to followup not reported/642 analyzed	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 Country Trial Name (Quality Score)	Results	Method of adverse event assessment
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 BPRS (Negative): 1 mg -0.8 (p<0.342); 2.5 mg -0.9 (p=0.417); 5 mg -0.5 (p=0.122) BPRS (Positive): 1 mg -2.8 (p<0.717); 2.5 mg -3.3 (p=0.167); 5 mg -2.6 (p=0.900); 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	Simpson-Angus Scale, AIMS, mobility (gait and balance) measured with Modified Performance-Oriented Mobility Assessment-II (POMA); spontaneously reported treatment-emergent adverse events.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Adverse events
de Deyn, 2004 Europe, Australia, Israel, Lebanon, and South Africa (FAIR)	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 Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria	Exclusion 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.	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 injetable 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.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Olanzapine (short-acting IM)					
Meehan, 2002 (Eli Lilly Study F1D-MC-HGHX) US, Russia, Romania (FAIR)	IM olanzapine 2.5 or 5 mg injection, given as 1, 2, or 3 injections over 24 hours	Not reported	Not reported	Mean age 77.6 years 92.3% white 61.0% female	% with dementia type not reported

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

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
Olanzapine (short-acting IM)				
Meehan, 2002 (Eli Lilly Study F1D-MC-HGHX) US, Russia, Romania (FAIR)	331/NR/272 enrolled	20/0/272	PANSS-Excited Component CMAI Agitation-Calmness Scale PANSS-dreived 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 Country Trial Name (Quality Score)	Results	Method of adverse event assessment
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	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 discontinuatino after randomization)

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Adverse events
Olanzapine (short-acting IM)	
Meehan, 2002 (Eli Lilly Study F1D-MC-HGHX) US, Russia, Romania (FAIR)	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 Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria	Exclusion criteria
Quetiapine					
Ballard, 2005 UK (FAIR)	93	26 weeks	Double-blind, multicenter	People with dementia living in care facilities in Newcastle. Those with clinically signfiicant agitation were referred by staff or physicia; eligible if CMAI total scroe >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 hehavior scales of the neuropsychiatric inventory; and no use of antipsychotics or acholinesterase inhibitors for 4 weeks before entry into the study.	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.
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.	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, cerebrovacular disorders, and abnormal ECG results). Psychotropic medications with few exceptions.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Quetiapine					
Ballard, 2005 UK (FAIR)	quetiapine 50 mg twice daily rivastigmine 9 mg daily placebo Titrated up to week 26	NR	NR	Mean age 83.8 (SD 7.7) 79.6% female Race/ethnicity NR	All had Alzheimer's Disease
Zhong, 2007 Full publication, replaces Zhong 2004, previously available as a poster only US (FAIR)	quetiapine 200 mg, quetiapine 100 mg or placebo.	Not reported	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

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

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
Quetiapine				
Ballard, 2005 UK (FAIR)	282/239/93	27/8/81	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)	Number screened, eligible not reported/ 333 enrolled	114 withdrawn/lost to followup not reported/# analyzed not clear	PANSS-EC (Excitement Component) CGI-C	Not reported

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Method of adverse event assessment
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)	Not reported
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)	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

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Adverse events
Quetiapine	
Ballard, 2005 UK (FAIR)	Not reported
Zhong, 2007 Full publication, replaces Zhong 2004, previously available as a poster only US (FAIR)	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).

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria	Exclusion 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.	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.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Trials of Risperidone					
Brodaty, 2003 Frank, 2004 Australia and New Zealand Brodaty 2005 (subgroup analysis) (FAIR)	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 psychotroppic medication was discontinued.	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

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

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
Trials of Risperidone				
Brodaty, 2003 Frank, 2004 Australia and New Zealand Brodaty 2005 (subgroup analysis) (FAIR)	Number screened not reported/384 eligible/345 enrolled	101 withdrawn/lost to followup not reported/304 analyzed	CMAI total agression 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 speicifcally trained raters and patients' primary caregivers. FAST and MMSE assessed at selection and week 12 (or last visit) M-NCAS completed by the nurse carer 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 Country Trial Name (Quality Score)	Results	Method of adverse event assessment
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 disturbancees): -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) M-NCAS mean change from baseline to endpoint (analysis on subgroup of 279 pa 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)	Monitoring the presence and severity of EPS at each visit and ratings on the Extrapyramidal Symptom Rating Scale.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Adverse events
Trials of Risperidone	
Brodaty, 2003 Frank, 2004 Australia and New Zealand Brodaty 2005 (subgroup analysis) (FAIR)	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 Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria	Exclusion 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.	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.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	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.	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

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

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
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	729 screened/625 eligible/625 enrolled	190/NR/617 analyzed	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.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Results	Method of adverse event assessment
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	Information regarding adverse events was obtained at each visit, Extrapyramidal Symptom Rating Scale.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Adverse events
Katz, 1999 US (FAIR) Katz, 2004 (subanalysis) Grossman, 2004 (subanalysis)	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

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	N	Duration	Study design Setting	Eligibility criteria	Exclusion criteria
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 moblie (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.	Patients excluded had recently been treated with neuroleptic injections, had other medical conditions that diminish cognition, or had other psychiatric disorders that produce psychotic sympotms. Patients with epilepsy, recent diagnoses or cancer (except nonmelanoma skin cancers), unstable medical conditios, changes in prescription medications 30 days before screening, or significant baseline laboratory or ECG abnormalities were also excluded.

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Interventions (drug, dose, duration)	Run-in/washout period	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)
Mintzer, 2006 US (FAIR)	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 psychotripic medications. Run-in length reduced for patients not using psychtropic medications and those whose psychosis or agitation worsened.	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

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

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
Mintzer, 2006 US (FAIR)	560/NR/473	117/1/416	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 Country Trial Name (Quality Score)	Results	Method of adverse event assessment
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	Simpson-Angus Scale, Barnes Akathisia Scale, AIMS

Evidence Table 16. Placebo-controlled trials in patients with behavioral and psychological symptoms of dementia

Author, year Country Trial Name (Quality Score)	Adverse events
Mintzer, 2006 US (FAIR)	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 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Main outcome	Study design	Study objective	Time period covered	Data source/ Inclusion criteria	Sample size
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	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
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	January 1, 1994-December 31, 2003	Pennsylvania state prescription-benefits program database; Pennsylvania Medicare	22,890 (39.9% conventional antipsychotics, 60.1% atypical antipsychotics)

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Population characteristics	Confounders adjusted for in study analysis	Results
Trifiro, 2007 The Netherlands	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.	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.
Wang, 2005 US	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	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 medicaitons, 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)

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Funder
Trifiro, 2007 The Netherlands	Not reported; no conflict of interest was declared
Wang, 2005 US	NIH, AHRQ

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Main outcome	Study design	Study objective	Time period covered	Data source/ Inclusion criteria	Sample size
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.	1999-2002	Medicaid data	18,987
Herrmann, 2004 Canada	CVAEs	Retrospective cohort	To examine the association between atypical antipsychotic use and stroke in the elderly	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)

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Population characteristics	Confounders adjusted for in study analysis	Results
Finkel, 2005 US	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	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 stdy medication was available in the post-index period; and an indicator fo 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
Herrmann, 2004 Canada	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	Hospitalizations, procedures, and drug utilization hyppothesized to be associated with the risk of stroke, demographic characteristics, and number of prescriptio 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)

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Funder
Finkel, 2005 US	Ortho-McNeil Janssen
Herrmann, 2004 Canada	No pharmaceutical industry support received for this study

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Main outcome	Study design	Study objective	Time period covered	Data source/ Inclusion criteria	Sample size
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.	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)
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	June 30, 1998-December 27, 1999	Systematic Assesssment 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
Percudani, 2005 Italy	CVAEs	Retrospective cohort	To investigate the relationship between exposure to second-generation antipsychotics and occurrence of cerebrovascular accidents in the elderly	2001	Regional database of hospital admissions and regional databse of prescriptions in one region in Italy (Lombardy)	35,604

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Population characteristics	Confounders adjusted for in study analysis	Results
Layton, 2005 England	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.	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)
Liperoti, 2005a US	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	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
Percudani, 2005 Italy	39.4% age 65-75, 38.7% 76-85, 22.0% over 85	Age, sex, number of antipsychotic prescriptions, and concomitant prescription of other drugs.	Adjusted OR (95% CI) for risk of cerebrovascular accidents Atypical antipsycotics 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)

Evidence Table 17. Observational studies in patients with behavioral and psychological symptoms of dementia

Author Year Country	Funder
Layton, 2005 England	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.
Liperoti, 2005a US	National Institute on Aging, National Institutes of Health
Percudani, 2005 Italy	Not reported

Evidence Table 18. Quality assessment of observational studies in patients with behavioral and psychological symptoms of dementia

	Internal validity				
Author, Year	**Non biased selecton**	**Loss to follow-up specified? If yes, low overall loss to follow-up?**	**Outcomes prespecified and defined?**	**Ascertainment techniques adequately described?**	**Non-biased and adequate ascertainment methods?**
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	Yes
Hien, 2005	Unclear - 46% participation rate	NR	Yes	Yes	Unclear - medical records review; no assessment of accuracy
Layton, 2005	Yes	Yes, 31-42% non-response rate	Yes	Yes	Unclear - depended on physician response to questionaire
Trifiro, 2007	Yes	Proportions left practice and impct on resulting duration of follow up NR	Yes	Yes	Yes

Evidence Table 18. Quality assessment of observational studies in patients with behavioral and psychological symptoms of dementia

				External validity	
Author, Year	**Statistical analysis of potential confounders**	**Adequate duration of follow-up**	**Overall quality rating**	**Was description of population adequate?**	**Sample size**
Finkel, 2005	Yes	3 months - defined by duration of RCTs reporting CVEs	Good	Yes	18,987
Hien, 2005	No control for dosage or duration of use	1 month	Fair-Poor	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
Layton, 2005	Age and sex only	up to six months exposure, but variable	Fair	No - Demographic characteristics for dementia subgroup NR, only for total cohort	Dementia cohort N=364
Trifiro, 2007	Yes	8 years	Good	Yes	N=2385

Evidence Table 18. Quality assessment of observational studies in patients with behavioral and psychological symptoms of dementia

Author, Year	Exclusion criteria	Funder
Finkel, 2005	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	Bed-bound; bilateral lower limb amputation; non-English speaking	National Health and Medical Research Council of Australia
Layton, 2005	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
Trifiro, 2007	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	Additional study eligibility criteria
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	At least one standardized measure such as a behaviour checklist used for the intervention and control group
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	Unpublished data or abstracts not included
Jesner, 2006 (Cochrane Review)	To determine the efficacy and safety of risperidone for people with autism spectrum disorder	1966-April 2006	Autism spectrum disorder	Risperidone only	Randomized controlled trials of risperidone vs placebo	Trials had to have at least one standardized outcome measure used for both intervention and control group

Evidence Table 19. Systematic reviews of atypical antipsychotics in youths

Author Year	Main results	Subgroups	Adverse events
Dinca, 2005	No quantitative synthesis. No informaiton on long-term effectiveness and safety. No data on quality of life. Risperidone (2 studies: McCracken 2002, McDougle 1998) effective in moderate-to-severe behavioraly 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	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 sudy (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.
Jesner, 2006 (Cochrane Review)	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); signficant 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

Evidence Table 20. Active-controlled 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	Allowed other medications/ interventions
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.	No

Evidence Table 20. Active-controlled trials of atypical antipsychotics in youths

Author, year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics (diagnosis, etc)	Number screened/ eligible/enrolled	Number withdrawn/ lost to fu/analyzed	Outcome measures
Olanzapine vs Haloperidol					
Malone, 2001 US (FAIR)	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.	Primary outcome: CGI Secondary outcome: Children's Psychiatric Rating Scale (CPRS)

Evidence Table 20. Active-controlled trials of atypical antipsychotics in youths

Author, year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Results
Olanzapine vs Haloperidol		
Malone, 2001 US (FAIR)	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

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							
Malone et al, 2001 US	Yes	Not reported	Yes	Yes	No	No	No
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					
Malone et al, 2001 US	Not reported	No	Yes	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**	**Class naïve patients only?**
Studies in children with Autism				
Active-control trials				
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.	Yes
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	No
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	NR

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Control group standard of care?	Funding	Comments
Studies in children with Autism			
Active-control trials			
Malone et al, 2001 US	Yes	Supported in part by a grant from Lilly Research Laboratories (Investigator-Initiated Study).	
Placebo-controlled trials			
Hollander, 2006 US double blind placebo-controlled Olanzapine Poor	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	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
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
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
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
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**	**Class naïve patients only?**
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	No
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.	No
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.	No

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Control group standard of care?	Funding	Comments
Nagaraj, 2006 India double blind placebo-controlled Risperidone Fair	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.]	
McCracken et al, 2002 Arnold et al, 2003 Research Units on Pediatric Psychopharmacology Autism Network RUPP	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.	
Shea et al, 2004 Pandina et al, 2004 (subgroup analysis) Canada	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
Snyder et al, 2002 Risperidone Conduct Study Group Canada, US, South Africa	Method not reported	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
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
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**	**Class naïve patients only?**
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.	Yes
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.	Yes
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.	NR

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	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	Supported by the Janssen Research Foundation.	
Snyder et al, 2002 Risperidone Conduct Study Group Canada, US, South Africa	Yes	Funded by Janssen Research Foundation	
Buitelaar, 2001 Netherlands	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?**
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
Findling et al, 2000 US	Yes	Yes	Trends: risperidone group older (p=0.006) and weighed more (p=0.12)	Yes	Yes	Yes	Yes
Armenteros, 2007 US	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
Reyes, 2006 International [8 countries, non-US] double blind placebo-controlled Risperidone Fair-Poor	Atrition, Yes Coss 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
Findling et al, 2000 US	Attrition and adherence yes, others no.	Withdrawals- 40% risperidone, 70% placebo	Yes	No	Fair
Armenteros, 2007 US	Yes, No, No, No	None	Yes	No	Good

Evidence Table 21. Quality assessment of trials in youths

	External Validity			
Author, year Country	**Number screened/eligible/enrolled**	**Exclusion criteria**	**Run-in/washout**	**Class naïve patients only?**
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	No
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.	No
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	No

Evidence Table 21. Quality assessment of trials in youths

Author, year Country	Control group standard of care?	Funding	Comments
Reyes, 2006 International [8 countries, non-US] double blind placebo-controlled Risperidone Fair-Poor	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.
Findling et al, 2000 US	Yes	Supported in part by the Janssen Research Foundation, the Stanley Foundation, and NICHD Pediatric Pharmacology Research Unit contract.	
Armenteros, 2007 US	Yes	First author has received research support and is on speakers panel of Janssen	

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 Aggressn Scale (OAS-M) rated by nurses in the ward at the end of the baseline phase; their aggressive behavior failed to responsd to behavioral treatment approaches; there was a clinical indicaton 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.	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	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.	
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) Biederman 2006 (post hoc subgroup analysis)	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.
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
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).
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.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Run-in/washout period
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.
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.

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
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).
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

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
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.
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

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
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 Akasthisia Scale, AIMS, query of parents or guardians	5/17 (29.4%) withdrew overall, no 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, Sinpson Angus Scale, and Barnes Akathesia Scale	3 overall/ 0 due to AEs

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Adverse events
Findling et al, 2000 US (FAIR)	No extrapyramidal symptoms
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 appetitie and sedation No abnormal movements, dyskinesias, or EPS

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
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, sterotypies, and language difficulties.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Run-in/washout period
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
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% borderlne 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
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 baselline, 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
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 moritored 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
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 hypersalivaton (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.

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 disorer.	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.

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, anticonvlsants, or antidepressants was not permitted.	Mean age 10.9 years 86.6% male 87% Caucasian	36.7% Conduct disorder, 60.9% Oppositionlal defiant disorder, 2.4% Disruptive behavior 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
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

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%)

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 appetitie, 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)

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
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
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
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
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
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
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.

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

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 inititated 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% placbebo 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%

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).

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.

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: riisperidone: 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.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
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).
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.

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Exclusions	Interventions	Run-in/washout period
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 ghte 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
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.

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
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 inititated 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
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)

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
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).
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.

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
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,a nd 12-lead ECG at baseline and endpoint.	2 of 55 (4%)/ 1 risperidone, 1 placebo
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

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	Adverse events
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 patitnes receiving risperidone.
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)

Evidence Table 22. Placebo-controlled trials in youths

Author, year Country Trial name (Quality score)	N	Duration	Study design setting	Population	Eligibility criteria
Troost, 2005 The Netherlands	24	8 weeks (placebo-controlled discontinuation phase)	Double-blind, single center	Pervasive developmental disorders	DSM-IV crieria for a pervasive developmental disorder. Patients were required to demonstrate clinically significant tantrums, aggressio, self-injurious behavior, or a combination of these problems. Age 5 to 17 years, a weight of at least 15 kg, and a mentalage 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
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 medicaitons.

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
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 monhts.	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
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
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
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).