Drug Class Review
on
Pharmacologic Treatments for ADHD

Final Report Update #2
Evidence Tables

November 2007

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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Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Preschool children			
Schleifer 1975 (Fair)	RCT DB crossover	Preschool children diagnosed as hyperactive participated in this study	NR
Barkley 1988 (Fair)	RCT DB crossover	1. Parent and/or teacher complaints of short attention span, poor impulse control and restlessness 2. Age of onset of problem behavior prior to 6 years 3. A duration of problem behavior for at least 12 months 4. Scores on the Hyperactivity Index of the Conners Parent Rating Scale and the Werry-Weiss-Peters Activity Rating Scale greater than two SDs above the mean for same-age, same-sex normal children 5. Scores on the Home Situations Questionnaire indicating that the child posed behavior problems in at least eight of the 16 situations described on the questionnaire to establish pervasiveness of behavior problems 6. Absence of epilepsy, severe language delay, deafness, blindness, autism, psychosis or gross brain damage as estabished through developmental/medical histories and observation of the children	NR
Musten 1997 Firestone 1998 (Fair)	RCT DB crossover	1. A diagnosis of ADHD based on DSM-III-R 2. A score greater than 1 on 8 out of 14 DSM-III-R items 3. A standard score greater than or equal to 80 on the Peabody Picture Vocabulary Test (PPVT) 4. A score equal to or above 1.5 SD above the age and sex mean of the Hyperactivity Index of the Conners Parent Rating Scale-Revised. 5. Attention span of less than 88 seconds on the parent-supervised attention task. 6. Parent and children were fluent in English 7. Subjects did not have any sensory or physical disatbilities, developmental disorders, neurologic disease, or obvious central nervous system dysfunction as assessed by a pediatrician. 8. Subjects who had received methylphenidate were considered for the study if they had received methylphenidate for less than 6 months and if the daily dosage administered was less than the mean of dosage used in the current study.	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Preschool children			
Schleifer 1975 (Fair)	methylphenidate: 2.5 mg - 20mg q.a.m and 10mg at lunch (mean dose = 5mg bid) Duration: 14-21 days	NR/NR	NR
Barkley 1988 (Fair)	methylphenidate 0.15mg/kg bid or 0.5mg/kg bid Duration: 7-10 days for each condition (baseline, placebo, low dose, high dose) Timing: NR	2 days/NR	NR
Musten 1997 Firestone 1998 (Fair)	methylphenidate 0.3mg/kg or 0.5mg/kg, bid Duration: 7-10 days for each condition (placebo, low dose, high dose) Timing: NR	2 days/ NR	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Preschool children		
Schleifer 1975 (Fair)	Observation Hyperactivity Rating Scale Timing: before and after the intervention	Mean age=4.08 years Gender: 89.3% male Ethnicity: NR
Barkley 1988 (Fair)	A free play (20 mins) and 5 task (20 mins total): mother-child interactions were videotaped and separate coding of the interactions was done using the Response Class Matrix. Timing: the last day of each drug condition	Mean age=3.9 years Gender: 70.3% male Ethnicity: NR
Musten 1997 Firestone 1998 (Fair)	Cognitive measures (Gordon Diagnostic System Delay and Vigilance Tasks) Behavior rating (CPRS-R) Observed behaviors Time on-Task Productivity Timing: at the end of the each treatment	Mean age=4.84 years Gender: 83.9% male Ethnicity: NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results
Preschool children				
Schleifer 1975 (Fair)	Mean IQ=102 (86-124) Hollingshead scale (socioeconomic class): Mean=2.5	NR/NR/28	0/2/26	Hyperactivity Rating Scale pre: active: placebo "True" Hyperactives (n=10): 50.80: 40.30:47.40 "Situational" Hyperactives: (n=16): 46.66: 32.75: 42.62 3-way ANOVA (group x condition x order) Active medication: F=29.09; p<0.01
Barkley 1988 (Fair)	the Peabody Picture Vocabulary Test: Mean=98.1(2.1), range 81-138 CPRS total: 68.4(25.4) CPRS hyperactivity: 19.6(5.0) Werry-Weiss-Peters Scale: 30(6.0)	NR/NR/27	0/0/27	Pairwise Comparison: Free play- only the low dose condition was significantly reduced as compared with the placebo condition, p<0.05 Task interaction -compliance: 15% improvement in high dose compared with placebo, p<0.05 -compete: 45% decrease occurred in off-task, or competing, behavior in high dose compared with placebo, p<0.05 Others: NS
Musten 1997 Firestone 1998 (Fair)	Peabody Picture Vocabulary Test (standard score)=99.26(14.41) Diagnostic Interview for Children and Adolescents (number)=12.03(1.49) Swansonm Nolan and Pelham Checklist (number)=11.48(1.91) Conners Hyperactivity Index (T score)=84.61(9.95) Attention Task-Supervised (sec)=30.43(10.36)	109(43 refused, 64 agreed) /54/41	4/6/31	Cognitive tasks: Gordon Delay: no. correct, P<L, P<H, p< 0.001; Efficiency ratio, NS Gordon Vigilance: no. correct, P<L, P<H, p<0.01; commission errors, NS Parent Rating Scale: Conners: learning, P>L, P>H, L>H, p<0.001; Conduct, P>L, P>H, p<0.001; Hyperactivity Index, P>L, P>H, p<0.001 Observed behaviors: Child compliance Task: %compliance, NS; Dot-to-Dot %compliance, NS; Cancellation Task %complaince, NS Time on-Task: Dot-to-Dot Task time, P<H, L<H, p<0.001; Cancellation task time, P<H, L<H, p<0.001 Productivity: Dot-to-Dot Task patterns correct, NS; Concellation Task rows correct, P<H, L<H, p<0.01

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Preschool children				
Schleifer 1975 (Fair)	NR	NR	0	
Barkley 1988 (Fair)	reported by mother	a tend (p<0.1) for the mothers to report more side effects during the medication than placebo conditions, but no in the severity of these side effects.	0	
Musten 1997 Firestone 1998 (Fair)	Side Effects Rating Scale (17 items)	placebo: low dose: high dose (%) <u>Temperament</u> Irritable: 81:75:38, P>H, L>H, p<0.001 Sad/unhappy: 47:56:84, P<H, L<H, p<0.001 prone to crying: 56:66:56, NS Anxous: 66:72:12, P>H, L>H, p<0.001 Euphoric/unusually happy: 19:25:6, NS <u>Somatic</u> Insomnia or trouble sleep: 59:62:42, P>H, L>H, p<0.05 Nightmares: 28:31:62, P<H, L>H, p<0.01 Stares a lot or daydreams: 47:47:52, NS Decreased appetite: 25:56:81, P<L, P<H, L<H, p<0.001 Stomachaches: 31:38:22, NS Headaches: 18.75:21.88:37.50, NS Drowsiness: 12.50:25:65.63, P<H, L<H, p<0.01 Bites fingernails: 12.5:15.63:28.13, NS Dizziness: 0:3.13:3.13, NS Tics or nervous movements: 3.13:9.38:12.50, NS <u>Sociability</u> Talks less with others: 21.88:34.38:50, P<H, p<0.05 Uninterested in others: 31.25:37.5:75, P<H, L<H, p<0.001	NR	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Conners 1975 (Poor)	RCT DB	Less than 6 years of age and not retarded and have a diagnosis of minimal brain dysfunction as manifested by: 1) hyperkinetic behavior; 2) a medical history of early onset of impulsive, restless, or agitated behavior; and 3) the presence of other symptoms such as short attention span, low frustration tolerance, easy distractibility, early rising from sleep, "driven" type of behavior, destructiveness of property, and aggressiveor disruptive play with peers or siblings. In addition, the child had to be physically healthy and free of gross sensory pathology, seizure disorder, and family psychopathology (including alcoholism, drug addiction, psychosis, or mental retardation)	80% of the children showed mild to moderate over-all dysfunction 0% was found to have major(focal) symptomatology 63% were found to have mild to moderate speech and language dysfunction 0% had marked movement disorders (synkinesis, dystonis, tremor, tics), but a majority had difficulty with fross body control. over 80% of the mothers refarded the children as overactive during their first two years of life
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	One year - 8 phases 1-week, open MPH treatment phase, followed by a 5-week, double-blind, placebo-controlled crossover trial; a 4-week, double-blind, placebo-controlled, parallel design phase; and 10-months' open maintenance. Setting NR	Stimulant naive, children of both sexes, ages 3 to 5.5 years with a DSM-IV consensus diagnosis of ADHD based on the Diagnostic Interview Schedule for Children IV-Parent Version and semistructured interview; combined or predominantly hyperactive subtype; an impairment scale score G55 on the Children`s Global Assessment Scale; hyperactive-impulsive subscale T score of 65 (1.5 SDs above the age- and sex-adjusted means) on both the Revised Conners Parent and Teacher Rating Scales; Full Scale IQ equivalent of 970 on the Differential Ability Scales; participation in a preschool, day care group setting, or other school program at least 2 half-days per week with at least eight same-age peers; and the same primary caretaker for at least 6 months before screening. Children were excluded if there was current evidence of adjustment disorder, pervasive developmental disorders, psychosis, significant suicidality, or other psychiatric disorder in addition to ADHD that required treatment with additional medication; current stimulant or cocaine abuse in a relative living in the home; a confounding medical condition; inability of the parent to understand or follow study instructions, or history of bipolar disorder in both biological parents. To be eligible, patients met both dimensional symptom criteria (scores 91.5 SD above age- and gender-adjusted means on the Hyperactive/Impulsive subscale of both parent and teacher Conners Rating Scales) and categorical diagnostic criteria (positive diagnosis on Diagnostic Interview Schedule for Children-IV and semistructured diagnostic interview).	Oppositional-defiant disorder; Communication disorder; Elimination disorder (i.e., encopresis, enuresis); Specific phobia (i.e., animals, needles, social phobia); Anxiety disorder (i.e., separation, generalized, posttraumatic□ stress disorder); Developmental coordination disorder; Conduct disorder; Pica; Adjustment disorder; Reactive attachment disorder; Obsessive-compulsive disorder; Sleepwalking disorder

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Conners 1975 (Poor)	methylphenidate Starting dosage: 5mg, bid (adjusted twice weekly) mean dose: 11.8(6.9)mg/day Duration: 6 weeks Timing: before the morning and midday meals	NR/NR	NR
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	Various- Methylphenidate (3.75 to 22.5 mg daily) vs. placebo , 70-week trial	1 Week	none

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Conners 1975 (Poor)	93-item behavior symptom list (before and after treatment) filled by parents. Clinical evaluation (week 2, 4, 6 after treatment): the Merrill-Palmer Intelligence Scale, the Beery-Buktenica Visual Motor Integration Test (VMI), the Flowers-Costello Test of centrak Auditory Abilities, the Meeting Street School Screening Test (MSST), Continuous Performance Test (CPT), the Harris-Goodenough Draw-a-Man Test, and Kagan's Matching Familiar Figures Test, Seat activity	Mean age=4.81 years Gender: 74.6% male Ethnicity: 100% white
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	For Phase 5: 5-Week Double-Blind, Placebo-Controlled, Crossover Design Titration Study a composite of parent and teacher ratings on commonly used behavioral scales Phase 6 4-Week, Double-Blind, Placebo-Controlled Parallel Study outcome derived from parent and teacher versions of the Swanson, Nolan, and Pelham Rating Scale, Version IV which measure both ADHD and oppositional defiant disorder symptoms and are sensitive to treatment effects. For adverse effects general clinician inquiry and parents and teachers rated AEs on a checklist based on the Pittsburgh Side Effect Rating Scale	Baseline n= 303 Mean age=4.41 yrs Gender: 76% male Ethnicity: 63% white 19% black 16% Hispanic or latino 2% Asian 0.7% other Phase 5-Crossover n = 165 Mean age=4.74 yrs Gender: 69% male Ethnicity: 63% white 18% black 18% Hispanic or latino 1% Asian 0.6% other Phase 6 Parallel n =114 Mean age=4.76 yrs Gender: 70% male Ethnicity: 65% white 17% black 17% Hispanic or latino 0.9% Asian 0.9% other

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results
Conners 1975 (Poor)	100% with upper-middle-class background 11(18.6%) had some prior analeptic therapy 2(3.4%) were able to sit quietly during the medical examination, 45% were extremely unmanageable 52% had a family history of hyperactivity	NR/66/59	3/0/56	Parent rating: Selected 18 items to be most related to hyperkinesis were analyzed, 4 out of 18 were significant improved in the drug group: disturbs other children, p<0.03; restless or overactive, p<0.01; throws himself around, p<0.05; always climbing, p<0.025 Activity chair: seat movement decrease, p<0.05; seat rotations, NS; feet movement, NS; total score, NS. Clinical evaluation (n=23, MPH=8, placebo=15): MSST: motor patterning improvement, NS; visual-perceptual-motor scores improvement, p<0.025; language raw score improvement, NS VMI: visual-perceptual-motor integration improvement, p<0.025 CPT: reduction in errors of omission, NS; reduction in errors of commission, NS. Merril-Palmer Intelligence Test: score improvement, p<0.01 Harris-Goodenough Draw-a-Man Test: IQ gain score improvement, NS MFFT: NS Flowers-Costiello Test of Central Auditory Abilities: total score, NS; competing messages test, NS Effects on Cortical Evoked Responses: increased amplitude for all visual and auditory amplitudes in drug condition, p<0.05
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	Conners Teacher rating scale (mean) Baseline 38.52 Phase 5 40.16 Phase 6 39.95 Conners Parent rating scale (mean) Baseline 35.43 Phase 5 35.91 Phase 6 35.48	Screened: 303 Eligible: 261 Enrolled: 183 and 165 randomized	1-week open-label lead-in (*n* = 183); a 5-week placebo-controlled, double-blind phase (*n* = 165); a 5-week double-blind, parallel phase (*n* = 114); and 10 months of open-label maintenance (*n* = 140 entered, 95 completed)	Phase 5 - decreases in ADHD symptoms were found on MPH vs. placebo at 7.5 mg (p < .01), 15 mg (p < .001), and 22.5 mg (p < .001) doses, but not for 3.755 mg (p < .06). The mean optimal MPH total daily dose for the entire group was 14.2 mg/day Parallel study phase 6, only 21% on best-dose MPH and 13% on placebo achieved MTA-defined categorical criterion for remission

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Conners 1975 (Poor)	Weight, BP, self-report	weight: NS BP: methylphenidate>placebo, p<0.07 other side effects: insomnia, anorexia, ataxia, nausea, headache, vomiting, jitteriness, sadness, cramps, thirst, rash, irritability, nightmares. The number of side effects in the drug group was not statistically exceed that in the placebo group	NR	
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	NR	Overall AEs per parents: 30% of parents reported moderate to severe AEs during study. MPH 15mg vs. placebo **Appetite decrease** chi-squared 5.4 P < 0.03 **Trouble sleeping** chi-squared 5.4 P < 0.03 MPH 22.5mg vs. placebo **Weight loss** chi-squared 4.0 P < 0.05 Severe AEs at baseline (2), open lead-in (23), titration (38), parallel (2), and maintenance (14) and overall there were 8 serious AEs throughout	Total withdrawals Parallel phase-placebo 45% MPH 15% Due to AEs Overall 11% (21) Open lead-in 11 Titration 3 Parallel Phase 1/114 Open label maintainence 7/140	Withdrawals were not reported well

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Adolescents: Head-to-head trials			
Cox 2006		Male and female active drivers who had ADHD and were aged 16 to 19 years were eligible to participate in the study. To be included in the study, adolescents had to have a diagnosis of current ADHD as determined by parent report, questionnaire, and structured clinical interviews; a positive history of stimulant responsiveness as disclosed by adolescents and parent reports; and current license to drive and reported daily driving activity. Adolescents were excluded when they had a history of tics or any adverse reactions to stimulant medication, a history of substance abuse disclosed by patient or parent, or a coexisting medical condition or medication usage that is known to interfere with the safe administration of stimulant medications.	Comorbid psychiatric diagnoses for 6 participants (1 agoraphobia, 1 conduct disorder with marijuana abuse, 1 with obsessive compulsive disorder, 1 with obsessive compulsive disorder and hypomania, and 2 with nicotine dependence).
Adolescents: Immediate release stimulants vs. placebo			
Brown 1988 (Fair)	RCT DB crossover	1. Receive a sexual maturity rating of at least 3 to thereby ensure postpubertal status 2. Diagnosed as having a long history of symptoms associated with attention deficit disorder based on DSM-III 3. Obtained a score of at least 15 on the Abbreviated Conners Teacher Rating Scale	NR
Pelham 1991 (Fair)	RCT DB crossover	Received a primary diagnosis of ADHD	15 met or exceeded criteria for Oppositional/Defiant Disorder (ODD) or Conduct Disorder (CD) based on DSM-III-R

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Adolescents: Head-to-head trials			
Cox 2006	OROS MPH, se-AMPH ER, or placebo Days 1 through 5, a half dose (36 mg/day OROS MPH or 15 mg/day se-AMPH ER), and on days 6 to 17, the full study dose of active drug (72 mg/day of OROS MPH or 30 mg/day of se-AMPH ER).	NR	21 were taking MPH , and 12 were taking amphetamine formulations.
Adolescents: Immediate release stimulants vs. placebo			
Brown 1988 (Fair)	methylphenidate 0.15mg/kg, 0.3mg/kg or 0.5mg/kg, bid (mean=4.38mg, 12.55mg, 21.28mg) Duration: 14 days for each condition (placebo, 0.15mg/kg, 0.3mg/kg and 0.5mg/kg) Timing: 8am and 12pm	none of the subjects had been treated with stimulants during the year procedind the study/ NR	NR
Pelham 1991 (Fair)	methylphenidate 0.3mg/kg to the nearest 1.25mg, bid mean dosage: 12.13mg (range 6.25mg-11.25mg) Duration: 4-11 days depending on the child Timing: morning at breakfast and midday	2 weeks/ NR	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Adolescents: Head-to-head trials		
Cox 2006	Driving stimulator at 5:00 PM, 8:00 PM, and 11:00 PM. Driving performance was rated by adolescents and investigators.	Mean Age 17.8 yrs Gender: 54% male Ethnicity: NR
Adolescents: Immediate release stimulants vs. placebo		
Brown 1988 (Fair)	Behavioral (at the end of each 2-week trial) Conners Parent Rating Scale-Revised (CPRS) Abbreviated Conners Parent (ACP) Teacher Hyperactivity Index (ATR) ADD/H Comprehensive Teacher Rating Scale (ACTeRS) Attention and impulsivity (1 hour after medication) Matching Familiar Figures Test(MFFT) Gordon Diagnostic System (GDS) Academic Arithmetic task Physiological (at least 1 hour after medication) Side Effect Rating Scale	Mean age=13.5 year Gender: 100% male Ethnicity: black
Pelham 1991 (Fair)	Daily behavior-modification point system Teacher-recorded classroom measures Teacher and counselor Conners rating scale Daily child's individual behavior and academic goals report card	Mean age=12.59 years Gender: 100% male Ethnicity: NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results
Adolescents: Head-to-head trials				
Cox 2006	Medication before study No medication 2 MPH formulations 21 Amphetamine formulations 12	Screened: NR Eligible: NR Enrolled: 35	35 analyzed	Overall driving performance was better with active treatment. a significant medication effect vs. placebo (F = 7.16, P < 0.001). Separate contrasts demonstrated that OROS MPH was associated with better driving performance than placebo (t = 3.31, P = .001) and se-AMPH ER (t = 2.15, P = 0.03), se-AMPH ER was not associated with better driving than placebo (t = 1.17, P < 0.24)
Adolescents: Immediate release stimulants vs. placebo				
Brown 1988 (Fair)	WISC-R IQ=92.91(5.28) Parent rating on Conners factoral rating scale(total)=0.91(0.33) Teacher ratins abbreviated Conners hyperactivity Index=2.12(0.36)	NR/NR/11	0/0/11	*28 out of 36 (75%) dependent measures resulted in significant main effects for drug condition Pairewise Comparison: placebo vs. 0.15mg/kg: 12/27(44%) items showed significant difference placebo vs. 0.30mg/kg: 14/27(52%) items showed significant difference placebo vs. 0.50mg/kg: 17/27(63%) items showed significant difference 0.15mg/kg vs. 0.30mg/kg: 5/27(18.5%) items showed significant difference 0.15mg/kg vs. 0.50mg/kg: 16/27(59.2%) items showed significant difference 0.30mg/kg vs. 0.50mg/kg: 6/27(22.2%) items showed significant difference
Pelham 1991 (Fair)	Mean IQ=97.2(11.0) DSM-III-R Structured Parent Interview: -ADHD symptoms: 10.6(2.5) -ODD symptoms: 5.7(2.3) -CD symptoms: 1.9(1.7) Abbreviated Cooners Rating Scale: -Parent: 21.4(4.4) -Teacher: 14.9(6.1) Iowa Conners Teacher Rating Scale: -I/O: 9.5(3.5) -A: 5.2(3.7) Woodcock-Johnson Achievement test: - Reading: 90.2(14.9)	NR/NR/17	0/0/17	Daily behavior-modification point system: 5 out of 6 items show the effect of drug, p<0.05 Teacher-recorded classroom measures: 4 out of 7 items show the effect of drug, p<0.05 Teacher and counselor Conners rating scale: 2 out of 2 items show the effect of drug, p<0.01 Daily child's individual behavior and academic goals report card, 1 out of 1 items show the effect of drug, p<0.01 9 out of 17(53%) adolescent were judged to be positive responders to 0.3mg/kg methylphenidate.

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Adolescents: Head-to-head trials				
Cox 2006	NR	One AE reported OROS MPH 36 urinary difficulty	No withdrawals but two participants rescheduled due to lack of adherence	
Adolescents: Immediate release stimulants vs. placebo				
Brown 1988 (Fair)	Side Effects Rating Scale	number of side effect: only a significant difference was found in the comarison of 0.15mg/kg and 0.50mg/kg	0	
Pelham 1991 (Fair)	NR	NR	0	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Varley 1983 (Fair)	RCT DB crossover	Patients with long-standing symptoms of impulsivity, short attention span, distractibility and excitability	100% were considered to have attention deficit disorder without hyperactivity or a conduct disorder.
Klorman 1986 Coons 1986 (Fair)	RCT DB crossover	Scored 1.5 on the abbreviated Conners Hyperactivity Questionnaire and 1.02 on the Home Activity Scale	NR
Smith 1998 Evans 2001 (Fair)	randomized, DB, cross-over	Adolescents diagnosed with ADHD (DSM-III-R), aged 12 and up, Verbal IQ >80, no conditions that precluded a trial of stimulants.	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Varley 1983 (Fair)	methylphenidate 0.15mg/kg, 0.3mg/kg, bid Duration: 1 week for each condition (placebo, low dose, high dose) Timing: 8am and 12pm	1 week/ NR	NR
Klorman 1986 Coons 1986 (Fair)	Week 1: 10mg at breakfast and lunch, 5mg at 4pm Week 2: 15mg at breakfast and lunch, 10mg at 4pm Week 3: 15mg at breakfast and lunch, 10mg at 4pm	2-4 weeks/NR	NR
Smith 1998 Evans 2001 (Fair)	25, 50 or 75 mg per day methylphenidate or placebo, 3 times per day, during weeks 3-8 of study.	2 week run in/ washout NR	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Varley 1983 (Fair)	Conners' abbreviated parent/teacher questionnaire Narrative comments regarding the subject Timing: daily	Mean age=14.27 years Gender: 77.3% male Ethnicity: NR
Klorman 1986 Coons 1986 (Fair)	Abbreviated Conners Questionnaire IOWA scale Sternberg Test Continuous Performance Test (CPT)	Mean age=14.80 years Gender: 84.2% male Ethnicity: NR
Smith 1998 Evans 2001 (Fair)	Timing of Assessment NR Omnibus test Linear trend 10-mg plateau 20 mg plateau quadratic trend	n= 46 mean age= 13.8 yrs 89% male 85% caucasian

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results
Varley 1983 (Fair)	All subjects had been noted to be stimulant responders. IQ mean=95.91, range 81-128	NR/NR/22	0/0/22	Dosage effects: Conners' Parent Questionnaire, parent narrative, Coners' Teacher Questionnaire, teacher narrative, all p<0.01 t test for correlated means (conners/ narrative) Parents -placebo vs low dose: p<0.05/ p<0.05 -placebo vs high dose: p<0.05/ p<0.05 -low dose vs high dose: NS/ p<0.05 Teachers -placebo vs low dose: p<0.05/ p<0.05 -placebo vs high dose: p<0.05/ p<0.05 -low dose vs high dose: NS/ p<0.05
Klorman 1986 Coons 1986 (Fair)	SES (hollingshead 4-factor): 2.32(1.01) Wechsler Full Scale IQ: 100.58(13.15) Peabody Individual Achievement Test: 93.47(12.43) Retrospective Conners Parent Scale: 1.96(0.48) Retrospective Home Activity Scale: 2.32(1.01) Current Conners Parent Scale: 1.52(0.62) Current Home Activity Scale: 1.76(0.96) Current Conners Teacher Scale: 1.35(0.69)	NR/NR/19	0/0/19	Parent rating (mean dose), placebo: methylphenidate Conners Scale= 1.35: 0.89, p<0.03 I/O=1.30: 0.89, p<0.05 A=1.36: 1.02, p<0.09 Teacher rating (mean dose), placebo: methylphenidate, all NS; Teacher rating (Week 3 dose), placebo: methylphenidate Conners Scale= 0.64: 0.50, NS I/O=0.82: 0.64, p<0.02 A=0.29: 0.16, p<0.02 Heart rate: rose under drug condition (100 beats/min), p<0.02 Sternberg Test: methylphenidate decreased errors and reaction time on performance, p<0.0001 CPT: methylphenidate reduced the rate of missed targets on performance, p<0.0001; enhanced the index of sensitivity of detection, p<0.0005; shorten P3b lantency, p<0.0001
Smith 1998 Evans 2001 (Fair)	Parent Iowa Conners Rating Scale (mean) Inattention/Overactivity: 10.1 Oppositional/Defiant: 8.5 Teacher IOWA Conners Rating Scale Inattention/Overactivity: 8.7 Oppositional/Defiant: 6.0 Disruptive behavior disorders parent rating scale Attention-deficit hyperactivity disorder: 8.8 Oppositional defiant disorder: 5.2 Conduct disorder: 1.7 Disruptive behavior disorders teacher rating scale Attention-deficit hyperactivity disorder: 7.5 Oppositional defiant disorder: 3.6 Conduct disorder: 1.9	screened NR/49 eligible/46 enrolled	0/0/46	**measure: mean score at 10mg MPH vs 20mg MPH vs 30mg MPH vs placebo** **C**onduct behavior frequency: 1.0 vs 0.21 vs 0.16 vs 3.7 Defiant behavior frequency: 11.4 vs 5.7 vs 4.3 vs 25.0 Teasing peers frequency: 1.1 vs 1.0 vs 0.9 vs 2.3 Impulsive behavior frequency: 8.3 vs 5.3 vs 4.4 vs 17.6 Inattention/Overactivity rating: 3.2 vs 2.7 vs 2.2 vs 4.2 Oppositional/defiant rating: 2.7 vs 2.3 vs 1.7 vs 3.9 Success Ratio (summary of negative behaviors): 92.6 vs 94.3 vs 95.5 vs 86.1 Job performance rating: 2.6 vs 2.4 vs 2.2 vs 2.8

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Varley 1983 (Fair)	NR	occasional comments regarding sleep disturbace and appetite suppression but none significant enough to warrant discontinuation of medication. There was a mean rise in the blood pressure of the subjects of 7mmHg in the diastolic, as well as an increase in the heart rate 10 beats/min in the high dose condition.	0	
Klorman 1986 Coons 1986 (Fair)	Subjects' Treatment Emergent Symptom Scale (STESS)	All 23 items showed no significant effect under drug condition: eat less, eat more, drink more, drink less, dry mouth, wet mouth, stomachache, nausea, rashes, headaches, dizziness, shakiness, pronuniciatrion, clumsiness, restlessness, fatigue, sleepiness, sleep problem, crying, irritability, unhappiness, sadness, inattention.	0	
Smith 1998 Evans 2001 (Fair)	patient, parent report	dulled affect, social withdrawal, stomachache, loss of appetite- ns at 10 mg, but increased at 20 mg and 30 mg. **Side effect/rater: 10 mg MPH vs 20 mg MPH 30 mg MPH vs placebo; p-value** Motor Tics Counselor: 0.3 vs 0 vs 0.4 vs 0; .693 Parent: 0.4 vs 0 vs 0.4 vs 0; .660 Tearful Counselor: 3.0 vs 3.3 vs 3.0 vs 6.4; .695 Parent: 2.2 vs 2.7 vs 2.3 vs 2.0; .943 Worried Counselor: 6.3 vs 4.9 vs 3.8 vs 5.5; .281 Parent: 1.8 vs 0.4 vs 2.7 vs 3.3; .556 Headache Counselor: 3.3 vs 3.4 vs 5.7 vs 3.8; .429 Parent: 1.6 vs 4.2 vs 3.03 vs 0.8; .093 Picking at skin, etc, Counselor: 13.4 vs 12.6 vs 13.4 vs 7.2; .099 Parent: 5.4 vs 4.0 vs 5.9 vs 0.4; .526 Buccal lingual movements Counselor: 4.0 vs 4.3 vs 2.7 vs 7.9; .030 Parent: 1.1 vs 0.4 vs 1.1 vs 8.4; ..848 Crabby Counselor: 13.4 vs 10.5 vs 9.4 vs 24.2; .000 Parent: 6.3 vs 5.0 vs 4.3 vs 8.4; .710 Dull/Tired/Listless Counselor: 6.5 vs 8.2 vs 12.4 vs 4.2; .001 Parent: 4.0 vs 4.4 vs vs 5.0 vs 1.8; .118 Withdrawn Counselor: 4.1 vs 4.1 vs 7.8 vs 0.7; .001	0	The clinical implications of this study are that, in most cases, the appropriate single dose of MPH for an adolescent with ADHD is between 10 mg-20 mg.

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	RCT DB crossover	Subjects received a DSM-III diagnosis of ADD in childhood as well as for the period preceding referral in separate interviews by a clinical psychologist of both the patient and his/her parent on the Diagnostic Instrument for Childhood nd Adolescence(DICA). Psychiatric diagnoses other than ADD were assigned if the DICA criteria were fulfilled for either the subject's or the parent's interview. The DICA as well as clinical evaluations by the physicians referring the patients to the study ruled out organic brain disorders or syndromes, childhood autism, psychosis, physical handicaps, and uncorrected visual or auditory deficits. Mental deficiency was ruled out by requiring Full Sclae WISC-R IQ scores > 80 on a test administerd within 6 months of referral. Subjects were in good physical health and free of all medication.	12(25%) Oppositional disorder plus conduct disorder 1(2.1%) tobacco dependence 5(10.4%) alcohol use 2(4.2%) alcohol abuse 1(2.1%) marijuana abuse 1(2.1%) history of major depression 16(33.3%) past or present adjustment disorder with affective mood 5(10.4%) overanxious disorder 5(10.4%) phobia 14(29.2%) enuresis in the present or past 3(6.3%) history of encopresis
Ahmann 2001 (Fair)	randomized, DB, cross-over	children aged 5-15 diagnosed with ADHD (DSM-III), ACTeRS Attention score at or below 25th percentile ACTeRS Hyperactivity Score at or below 25th percentile CTRS-28 Inattention/Passivity Scale 2 or more sd above mean CTRS-28 Hyperactivity Index 2 or more sd above mean CPRS-48 Hyperactivity Index 2 or more sd above mean met the criteria of a Ritalin responder: parent reported 1 sd improvement on CPRS-48 Hyperactivity Index, or 1 positive narrative, teacher reported same scores	NR
Adolescents: Longer-acting stimulants vs. placebo			
Spencer 2006	Randomized, DB, parallel study, multicenter	Adolescents aged 13 to 17 years, weighing ≤75 kg (≤165 lb), who satisfied DSM-IV-TR 1 criteria for primary diagnosis of ADHD combined subtype (predominantly inattentive subtype or hyperactive-impulsive subtype), were eligible for the study. Key inclusion criteria were an intelligence quotient score≥80, normal blood pressure (girls--systolic blood pressure, 128-132 mm Hg; diastolic blood pressure, 84-86 mm Hg; boys--systolic blood pressure, 130-140 mm Hg; diastolic blood pressure, 84-89 mm Hg), electrocardiographic (ECG) findings within the normal range, and a willingness and ability to comply with protocol requirements in conjunction with a parent or caregiver. Adolescents who were known to be nonresponsive to stimulants (defined as no clinical improvement after trials of 2 stimulant medications, taken for at least 3 weeks each) or naive to stimulant treatment were eligible for enrollment. Exclusion criteria included comorbid illness that could interfere with study participation or impact the efficacy and tolerability of MAS XR; a history of nonresponse to stimulant medication; a d	Oppositional defiance disorder not excluded

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	weight <37.5kg: week 1-- 7.5mg bid in the morning and at noon week 2-- 10mg bid in the morning and at noon week 3-- 10mg in the morning and at noon and 5mg at 4pm weight between 37.5-54kg: each of the above doses was incremented by 2.5mg weight >54kg: each of the above doses was incremented by 5mg Duration: 1 week for each condition(baselind, placebo, drug) Mean dosage: 35.33mg/day, or 0.64mg/kg/day	NR/NR	NR
Ahmann 2001 (Fair)	0.3 mg/kg and 0.5 mg/kg doses, and placebo, 3 times per day, in 7 day cycles, in 2 weeks trials.	run-in NR, no washouts due to short half-life of ritalin	NR
Adolescents: Longer-acting stimulants vs. placebo			
Spencer 2006	Forced-dose titration MAS XR (10-40 mg/day); Adderall XR vs. placebo MAS XR groups: 10 mg/day MAS XR for 4 weeks 20 mg/day MAS XR (10 mg/day week 1, 20 mg/day weeks 2-4) 30 mg/day MAS XR (10 mg/day week 1, 20 mg/day week 2, 30 mg/day weeks 3-4) 40 mg/day MAS XR (10 mg/day week 1, 20 mg/day week 2, 30 mg/day week 3, 40 mg/day week 4)	1-4 week washout phase depending on ADHD medication	NR

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	Abbreviated Conners Hyperactivity Questionnaire, weekly IOWA scale, weekly Open-end questions, weekly Hyperactivity, Attention, and Aggression Scale of the Time on Task Scale (TOTS), at the end of each phase Global outcome, in the last session Continuous Performance Test (CPT)	Mean age=14.12 years Gender: 87% male Ethniciry: 96% Caucasian
Ahmann 2001 (Fair)	Weekly completion of (BSEQ) Barkley Side Effects Questionnaire, by parents.	n=79 ethnicity NR ages 10-15y 79.7% males
Adolescents: Longer-acting stimulants vs. placebo		
Spencer 2006	Change from baseline in ADHD-RS-IV score ADHD-RS-IV scores analyzed post hoc in low and high baseline ADHD-RS-IV severity groups Score on CGI-I scale	Mean age 14.2 years 65.5% male 73.7% white 15.8% black 6.8% Hispanic 3.6% other

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	Hollingshead 4-point SES=51.33(14.29) WISC-R full scale IQ=109.54(12.10) PIAT age total score=99.50(12.08) Home Activity Scale by parent: contemporaneous=1.35(0.94); retrospective=1.74(0.89) Conners Hyperactivity scale: contemporaneous(parent)=1.21(0.62); retrospective(parent)=1.39(0.67); contemporaneous=1.28(0.52)	NR/NR/48	NR/NR/48	Significant improvement in drug condition: Abbreviated Conners Hyperactivity Questionnaire, by parent: p<0.0005; by teacher: p<0.0005 I/O scale, by parent: p<0.002; by teacher: p<0.005 Aggression scale, by parent: p<0.006; by teacher: p<0.0002 valence of comments, by parent: p<0.007; by teacher: p<0.0001 *Parents detected sigificantly less disturbance over week, p<0.003 *Teachers reported greater improvement as dosage increased over the course of the methylphenidate phase, p<0.03 *Teachers reported greater improvement for younger than older patients in aggression ratings. TOTS scales: improvement under drug condition, p<0.02 (over all) -rated by parent, in aggression, p<0.03; hyperactivity, p=0.05; attention, p=0.06 -rated by teacher, in aggression, p<0.03, hyperactivity, p<0.0002; attention, p<0.04 Global outcome: improvement under drug condition, p<0.006 CPT: improvement in accuracy and speeded reaction times to targets, p<0.05
Ahmann 2001 (Fair)	NR	NR/NR/NR	NR/NR/79	**Barkley Side Effects Questionnaire Scores** Ritalin vs placebo, p value Insomnia: 51.3 vs 26.3, p<0.001 Decreased appetite: 61.8 vs 25.0, p<0.001 Stomachache: 36.8 vs 14.5, p<0.001 Headache: 38.7 vs 22.7, NS Dizziness: 10.7 vs 1.3, NS Daydreaming: 42.7 vs 52.0, NS Irritability: 62.2 vs 80.3, p<0.01 Anxiety: 50.7 vs 64.0, NS Nailbiting: 26.7 vs 36.0, NS
Adolescents: Longer-acting stimulants vs. placebo				
Spencer 2006	78.8% patients were treatment naïve	Screened: 287 Eligible: 287 Enrolled: 287 Placebo = 54 MAS XR 10 mg/day = 56 MAS XR 20 mg/day = 56 MAS XR 30 mg/day = 58 MAS XR 40 mg/day = 63	Withdrawn 23; MAS XR 21, placebo 2 Lost to f/u 6 Analyzed 278 Placebo = 52 MAS XR 10 mg/day = 54 MAS XR 20 mg/day = 53 MAS XR 30 mg/day = 58 MAS XR 40 mg/day = 61	Improvement in mean ADHD-RS-IV total scores in all 4 MAS XR groups compared with placebo (p<0.001) at all weeks Mean change from baseline was -17.8 in MAS XR 10 to 40 mg/day groups and -9.4 in placebo group Greater improvements observed in low baseline severity groups for MAS XR 20, 30, and 40 mg/day than placebo ($p \leq 0.01$)and in all MAS XR groups with high baseline severity than placebo ($p \leq 0.02$) Higher % improved in endpoint CGI-I scale in MAS XR groups than placebo (p<0.01)

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	Subjects' Treatment Emergent Symptom Scale (STESS)	Appetite loss: by parent, 0.05; by patient, p<0.001 Increased thirst: NS Dry mouth: by parent, NS; by patient, p<0.1 Stomachaches: NS Nausea: NS Headaches: NS Sleep problem: NS Shakiness: by parent,NS; by patient, p<0.1 Crying: NS Anger: NS Unhappiness: NS Sadness: NS	0	
Ahmann 2001 (Fair)	patient/parent report	"dazed", with rapid heartbeat and difficulty breathing: n=1 "zombie": n=1 stomachache, headache, decreased appetite and insomnia: n=1 decreased appetite and sleep problems: n=1	4 withdrawals, all due to adverse events.	the study includes the largest group of girls with ADHD reported in the literature (n=45)
Adolescents: Longer-acting stimulants vs. placebo				
Spencer 2006	AEs, vital signs, and body weight recorded at weekly study visits and 30 days after drug discontinuation AEs categorized as mild, moderate, or severe ECGs at screening and endpoint	MAS XR/ placebo anorexia, decreased appetite 35.6%/ 1.9% headache 16.3%/ 22.2 % insomnia 12.0%/ 3.7% abdominal pain 10.7%/ 1.9% weight loss 9.4%/ 0% 97.5% AEs mild or moderate in intensity	Total withdrawn 23 Withdrawn AE 5 MAS XR, 0 placebo	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Wilens 2006	Multisite study (15 sites) consisting of 4 phases. 1-week washout phase, an open-label dose titration phase lasting up to 4 weeks, a 2-week double-blind phase and an 8-week open-label follow-up safety phase assessing treatment	Adolescent outpatients aged 13 to 18 years having a diagnosis of ADHD (any subtype) were eligible for the study. Diagnosis of ADHD was based on a clinical evaluation using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSMIV) criteria, confirmed by structured interview (using the behavior module of the Kiddie Schedule for Affective Disorders and Schizophrenia) and by a Children's Global Assessment Scale score of 41 to 70. Eligible subjects could be taking no medications for ADHD at the time of enrollment. Subjects using a behavioral modification program at the time of enrollment had to agree not to change the program or initiate a new program during the study period. Participants had to comply with the study visit schedule, and their parents or caregivers had to be willing to complete all assessments. Excluded subjects included any adolescents with a history of nonresponse to methylphenidate treatment, hypersensitivity or significant intolerance to methylphenidate, clinically significant gastrointestinal tract problems, clinically important electrocardiographic or blood pressure measurement abnormalities, or coexisting medical conditions or concurrent medications likely to interfere with the safe administration of methylphenidate. Subjects requiring any of the following medications were excluded: clonidine or other α2-adrenergic receptor agonists, tricyclic antidepressants, selective serotonin reuptake inhibitors, theophylline, warfarin sodium, and anticonvulsant agents. Participants with psychiatric comorbidities were eligible for inclusion, except for those with Tourette syndrome or a family history of Tourette syndrome, an ongoing seizure disorder, bipolar disorder, psychotic disorder, a mood or anxiety disorder requiring drug therapy, alcohol or other drug abuse within the 6 months before study enrollment, an eating disorder, or marked anxiety, tension, or agitation.	Participants with psychiatric comorbidities were eligible for inclusion, except for those with Tourette syndrome or a family history of Tourette syndrome, an ongoing seizure disorder, bipolar disorder, psychotic disorder, a mood or anxiety disorder requiring drug therapy, alcohol or other drug abuse within the 6 months before study enrollment, an eating disorder, or marked anxiety, tension, or agitation.
Buitelaar 2007	RCT Europe (24 centers), Israel (2 centers), South Africa (4 centers), and Australia (3 centers)	Patients aged 6 to 15 years who met DSM-IV criteria for ADHD, as assessed by clinical history and confirmed by a structured interview (Schedule for Affective Disorders and Schizophrenia for School-aged Children-Present and Lifetime Version [K-SADS-PL]), and whose symptom severity was at least 1.5 standard deviations above US age and sex norms on the ADHD Rating Scale IV (ADHD RS) were eligible to participate. Patients with bipolar disorder or psychotic illness were excluded, as were patients with unstable medical illness or conditions requiring ongoing administration of a psychoactive medication (other than atomoxetine). Comorbid psychiatric disorders were assessed clinically and by the K-SADS-PL.All subjects had a medical evaluation including physical examination, routine chemistries, liver function tests, complete blood count, urinalysis, and electrocardiogram (ECG).	NR
Adolescents: Atomxetine vs. placebo			

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule		Run-in/Washout Period	Allowed other medications/ interventions
Wilens 2006	methylphenidate, osmotic-release oral system(OROS) day 11-14 weeks	18-72 mg	1 Week	none
Buitelaar 2007	Atmoxetine vs. placebo	6 months	NA	None
Adolescents: Atomxetine vs. placebo				

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Wilens 2006	ADHD RS, Conners-Wells Adolescent Self-report of Symptoms Scale, and CCI, as well as changes inheart rate and systolic and diastolic blood pressure from baselineto the end of the double-blind phase of the study CGI -I at end of double blind period only	Mean age=14.6 yrs Gender: 80.2% male Ethnicity: 75.1% white 13.6% black 11.3% other
Buitelaar 2007	investigator-administered version of the ADHD RS, CGI-S, Child Health Questionaire, relapse rates	Mean age=10.8 yrs Gender: 90% male Ethnicity: NR
Adolescents: Atomxetine vs. placebo		

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results
Wilens 2006	ADHD RS score investigator 31.26 parent 30.82 Parent Child Conflict Index 0.272 Conners-Wells Adolescent Self-report of Symptoms Scale 91.96	Screened: NR Eligible: NR Enrolled: 220	49/ NR/ 220	Change in measures from baseline to end of double blind period of active vs. placebo DHD RS Investigator -14.93 vs. -9.58 P = 0.001 parent -14.00 vs. -10.14 P = 0.008, Conners-Wells Adolescent Self-report of Symptoms Scale -31.7 vs. -18.7 P= 0.001 and CCI -0.098 vs. -0.016 P= 0.005 CGI-I much or very much improved 51.8% vs. 31.0% P= 0.01
Buitelaar 2007		Screened: NA Eligible: NA Enrolled: 163	41/ NR/ 161	Change from baseline active vs placebo Rates of relapse 2.5% vs. 12.2% (P = NR) ADHD-RS 1.7 vs. 7.8 (P < 0.001) RR for relapse during placebo trmt 5.6 (95% CI 1.2, 25.6)
Adolescents: Atomxetine vs. placebo				

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Wilens 2006	NR	Active vs placebo (%) **headache** 3.4 vs. 6.7 **decreased appetite** 2.3 vs. 0 **insomnia** 4.6 vs. 0 **abdominal pain** 1.1 vs. 2.2 **nausea** 1.1 vs. 2.2 **asthenia** 0 vs. 2.2 **diarrhea** 2.3 vs. 0 for all P = NR	During double-blind phase- Withdrawals active 18% placebo 31% Due to AEs active 1% placebo 0%	
Buitelaar 2007	NR	NR	Total 27% atomoxetine 17.7% placebo 33.3% Due to AEs NR	
Adolescents: Atomxetine vs. placebo				

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Wilens 2006		Subjects were children (younger than 12 years old) and adolescents (12 years old and older) recruited by referral and advertisement. The cutoff age of 12 for children versus adolescents was used in regulatory submissions of atomoxetine. All of the subjects met diagnostic criteria for DSM IV–defined ADHD (any subtype) as assessed by clinical history and structured interview. In five studies, subjects were required at study entry to have an ADHD symptom severity score at least 1.5 SDs above U.S. age and sex norms, as measured by the ADHD Rating Scale, and in one study, severity scores had to be 1.5 SDs above norms on the Conners Parent Rating Scale- Revised: Short Form and 1.0 SD on the ADHD RS-Teacher Version. Exclusion criteria included an IQ <80, as assessed by the WISC-III; any serious medical illness, comorbid psychosis, or bipolar disorder; history of a seizure disorder, or ongoing use of psychoactive medications other than the study drug. One of the six studies was a dose-response study that included a fixed, low-dose atomoxetine arm (0.5 mg/kg/day). Subjects assigned to this arr analysis because these subjects did not have the opportunity to reach atomoxetine exposures sufficient to achieve optimal efficacy or maximum risk for adverse events and were therefor not comparable with the other subjects.	

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Wilens 2006			

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Wilens 2006		

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Results
Wilens 2006				

Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Wilens 2006				

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	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?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Preschool chidren									
Schleifer 1975	NR	NR	n/a	Yes	Yes	Yes	Yes	No No No No	NR NR
Barkley 1988	NR	NR	n/a	Yes	Yes	Yes	Yes	No No No No	NR NR
Musten 1997 Firestone 1998	NR	Yes	n/a	Yes	Yes	Yes	Yes	Yes No No No	No No
Conners 1975	NR	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	No No

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Preschool chidren					
Schleifer 1975	Yes	No	Fair	NR/NR/28	NR
Barkley 1988	Unclear	No	Fair	NR/NR/27	NR
Musten 1997 Firestone 1998	No; Analysis excluded 10 patients (24%) - 4 "withdrew" and 6 "did not have completed assessment protocols"	No	Fair	109 (43 refused, 64 agreed) /54/41	NR
Conners 1975	No; different numbers of patients were excluded from analyses at each time point due to "missing data"	No	Poor	NR/66/59	Marked anxiety, tension, or agitation thought to result from current psychological stress in the home; hypersensitivity to MPH; glaucoma; epilepsy; severe organic brain damage; or need during therapy for any other psychotropic drugs; pressor agents, MAO inhibitors, phenybutazone, or coumarin-type anti-coagulants

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Preschool chidren					
Schleifer 1975	No No	No	Yes	Supported in part by a Dominion-Provincial Mental Health grant to Dr. Gert Morgenstern	Yes
Barkley 1988	NR/NR	No	Yes	NIMG Grant # MH 32334; Department of Neurology, Medical College of Wisconsin	Yes
Musten 1997 Firestone 1998	NR/NR	No	Yes	Health Canada grant 6606-4979-63	Yes
Conners 1975	NR/NR	No	Yes	In part by U.S. Public Health Service research grant # MH 18909 from the National Institute of Mental Health	Yes

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	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?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
PATS (Greenhill 2006, Kollins 2006, Wigal 2006)	Method not reported	Yes	Unclear	Yes	Yes	NA	Yes	Yes Yes Yes Yes	Yes Enrolled in crossover titration trial: 165 Enrolled in parallel trial: 114

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
PATS (Greenhill 2006, Kollins 2006, Wigal 2006)	No	Yes	Fair, despite high attrition (due to extra cautious safety measures).	1915/553/303	Child or parent could not understand or follow instructions, evidence of moderate to severe adverse effects or evidence of much improved response to any dose of methylphenidate or another stimulant, >5 week exposure to at least 30 mg/day of methylphenidate or equivalent doses or other stimulants, use of any other psychotropic medication, taken investigational drug in last 30 days, history of motor or vocal tics or Tourette's syndrome, major medical conditions that would interfere with involvement in long-term study or could be negatively affected by study drug, current evidence of adjustment disorder, autism, psychosis, significant suicidality, or other psychiatric disorder in addition to ADHD that requires medication, evidence of current physical, sexual, or emotional abuse, living with anyone abusing stimulants or cocaine, or history of bipolar disorder in both biological parents. Also, ADHD improvement after required parent behavior training.

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
PATS (Greenhill 2006, Kollins 2006, Wigal 2006)	No Yes	NR	Yes	National Institutes of Mental Health; Author's relationships with Pharma are disclosed (long list)	

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	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?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Adolescents									
Brown 1988	NR	NR	n/a	Yes	Yes	Yes	Yes	No No No No	NR NR
Pelham 1991	NR	NR	n/a	Yes	Yes	Yes	Yes	No No No No	NR NR
Varley 1983	Yes	NR	n/a	Yes	Yes	Yes	Yes	Yes No No No	No No
Klorman 1986 Coons 1986	NR	NR	n/a	Yes	Yes	Yes	Yes	No No No No	NR NR
Smith 1998 Evans 2001	NR	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	NR NR

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Adolescents					
Brown 1988	Unclear	No	Fair	NR/NR/11	Mentally retardation or gross neurological disorders
Pelham 1991	Unclear	No	Fair	NR/NR/34	Mental retardation or gross neurological disorders
Varley 1983	Yes	No	Fair	NR/NR/22	Conduct disorder
Klorman 1986 Coons 1986	Unclear	No	Fair	NR/NR/19	(1) No evidence of organic brain disorder, psychosis, or uncorrected sensory impairment; (2) Full-Scale WAIS-R or WISC-R IQ scores of at least 74; and (3) no treatment with drugs for a suitable period before entering the protocol, 2 weeks for patients receiving MPH and 4 weeks for those also receiving thioridazine
Smith 1998 Evans 2001	Unclear	No	Fair	NR/NR49	NR

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Adolescents					
Brown 1988	NR/NR	NR	Yes	NR	Yes
Pelham 1991	NR/NR	NR	Yes	NR	Yes
Varley 1983	NR/NR	No	Yes	NR	Yes
Klorman 1986 Coons 1986	NR/Yes (see exclusion criteria)	No	Yes	NIMH Grants MH 32103 and MH38118	Yes
Smith 1998 Evans 2001	Run-in: NR Wash-out: 2 weeks prior to randomization	No	Yes	National Institute on Drug Abuse, NIMH, National Institute on Alcohol Abuse and Alcoholism, and the National Institute of Child Health and Human Development	Yes

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	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?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Klorman 1990 Klorman 1991 Klorman 1992	NR	NR	NR	Yes	Yes	Yes	Yes	No No No No	NR NR
Bostic 2000	NR	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	NR NR
Ahmann 2001	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes No No No	NR NR
Cox 2006	Yes	NR	NR	Yes	Yes	NA	Yes	No No No No	No No

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Klorman 1990 Klorman 1991 Klorman 1992	Unclear	No	Fair	NR/NR/48	CNS involvement, childhood autism, psychosis, physical handicaps, and uncorrected visual or auditory problems, mental deficiency
Bostic 2000	Yes	No	Fair	32/21/21	Clinically significant medical conditions or abnormal baseline laboratory liver function tests, mental retardation, organic brain disorders, unstable psychiatric conditions, bipolar disorder, psychosis, drug or alcohol abuse of dependence withint the prior 6 months, or active pregnancy or nursing.
Ahmann 2001	No	No	Fair	NR/NR/234	History of seizures, mental retardation, Tourette's syndrome, or other significant neurologic history
Cox 2006	NR	No	Poor	NR/NR/35	History of tics, any adverse reactions to stimulant medication, history of substance abuse, or coexisting medical condition or medication usage known to interfere with safe administration of stimulant medications

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Klorman 1990 Klorman 1991 Klorman 1992	NR NR	95.8% treatment naïve	Yes	NIMH grant MH38118	
Bostic 2000	No Patients on psychotropics were required to washout at least 2 weeks before the beginning of the study; treatment periods were separated by 2-week washout period	NR	Yes	Eli Lilly, Inc.	Yes
Ahmann 2001	No No	NR	Yes	Marshfield Clinic grants 0844-01-87 and 0844-01-90	Yes
Cox 2006	No No, even with cross-over design	NR	NR	McNeil Pediatrics Division of McNeil-PPC, Inc.	Is effect of drug on *driving performance* relevant? All subjects

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	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?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Spencer 2006	Method not reported	NR	Unclear	Yes	Unclear, although says "double-blind" in title	Unclear, although says "double-blind" in title	Unclear, although says "double-blind" in title	Yes NA Yes No	No No
Wilens 2006	Yes	Yes	Yes, except more males in C vs I	Yes	Yes	NA	Yes	Yes NA Yes No	Yes I: 16/87 C: 28/90

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Spencer 2006	Yes	Yes	Fair	335/308/297	Comorbid psychiatric diagnosis (except ADHD), diagnosis of conduct disorder, medical history of nonresponse to stimulant medication, seizures, tic disorder, or Tourette's syndrome
Wilens 2006	Yes	Yes	Good	220/182/175	History of nonresponse to methylphenidate treatment, hypersensitivity or significant intolerance to methylphenidate, clinically significant gastrointestinal tract problems, clinically important electrocardiographic or blood pressure measurement abnormalities, coexisting medical conditions, concurrent medications likely to interfere with safe adminstration of methylphenidate, Tourette's syndrome, family history of Tourette's syndrome, ongoing seizure disorder, bipolar disorder, psychotic disorder, mood or anxiety disorder requiring drug therapy, alcohol or other drug abuse within 6 months before enrollment, eating disorder, marked anxiety, tension, agitation, or requiring any of the following medications: clonidine or other adrenergic receptor agonists, tricyclic antidepressants, selective serotonin reuptake inhibitors, theophylline, warfarin sodium, and anticonvulsant agents.

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Spencer 2006	No Yes	NR	NR	Shire Pharmaceuticals Inc.	Is comorbid ADHD and ODD (Oppositional Defiant Disorder) relevant?
Wilens 2006	No Yes	No	Yes	McNeil Consumer and & Specialty Pharmaceuticals	

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

	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?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**
Buitelaar 2007	Yes	NR	Unclear	Yes	Yes	Yes	Yes	Yes NA No No	Yes I: 65/79; C: 54/81

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

				External Validity	
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Buitelaar 2007	No	Yes	Fair	604/NR/163	Bipolar disorder, psychotic illness, unstable medical illness, or conditions requiring ongoing administration of psychoactive medication (other than drug under investigation)

Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Buitelaar 2007	NR Yes	No	Yes	Eli Lilly and Co.	Is assessment long-term, continuation treatment relevant?

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Dextroamphetamine vs. methylphenidate IR			
Arnold 1978 Huestis 1975 Fair	RCT with crossover Single center	Diagnosis of Minimal Brain Dysfunction with such signs an symptoms as hyperactivity, short attention span, distractibility, irritability, variability, explosiveness, aggression, inability to keep friends or function in a group, underachievement, visual-motor dysfunction, and poor coordination or other minor neurological signs; total score of 24 or more on the first six items of the Davids Hyperkinetic Rating Scale, by parents and teacher; indication for stimulant treatment as determined by the patient's psychiatrist; aged between 5 and 12 years; enrollment in some sort of school setting to obtain teachers' ratings; no psychoactive drug in the preceding month; iinsufficient benefit from an initial 2-week "placebo washout" to be maintained without active drug	NR
Efron 1997 Australia Fair	RCT with crossover Single center	Age between 5 and 15 years; meet DSM-IV criteria for ADHD. The DuPaul ADHD rating scale was used; each DSM-IV ADHD symptom was marked on a 4-point scale: "never or rarely," (0); "sometimes," (1); "often," (2); and "very often," (3). Only symptoms rated 2 or 3 were considered present and counted toward the diagnosis; T-score of at least 1.5 standard deviations (SD) above the mean on the Attention Problems scale of the Child Behavior Checklist or Teacher Report Form. No history of intellectual disability, gross neurologic abnormality, or Tourette's syndrome. Decision made to trial stimulant medication on clinical grounds.	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Dextroamphetamine vs. methylphenidate IR	
Arnold 1978 Huestis 1975 Fair	Days 1/2/3+: Dextroamphetamine: 5/10/15 mg Methylphenidate: 10/20/30 mg 3 weeks, then crossover Twice daily: morning and noon
Efron 1997 Australia Fair	Dextroamphetamine 0.15mg/kg Methylphenidate 0.3 mg/kg Both rounded off to the nearest capsule size x 2 weeks then crossover

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Dextroamphetamine vs. methylphenidate IR				
Arnold 1978 Huestis 1975 Fair	2-week placebo washout	NR	Parents' Symptom Checklist (Arnold and Smeltzer) Conners Teachers' Behavior Checklist; Davids' Hyperkinetic Rating Scale (completed by both parents and teachers); target symptom assessment/quantification using 9-point scale (1=excellent, 5=no change from placebo washout; 9=disastrous)	Mean age=8 75.9% male Race nr
Efron 1997 Australia Fair	24-hour washout	NR	Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III), 28-item Conners' Teacher Rating Scale-Revised (CTRS-R), 48-item Conners' Parent Rating Scale-Revised (CPRS-R), Continuous Performance Test (CPT), Child Behavior Checklist (CBCL)	8.7 years NR NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Dextroamphetamine vs. methylphenidate IR			
Arnold 1978	Mean sum CTRS=91.52	NR	NR
Huestis 1975	CTRS factor I (conduct)=35.83	NR	NR
	CTRS factor IV (hyperactivity)=23.10	29	29
Fair	Mean total items 1-6 DHRS by teachers=29.03 DHRS by teachers Item I (hyperactivity)=5.28 Mean total items 1-6 DHRS by parent=30.76 DHRS by parent Item I (hyperactivity)=5.24 Mean sum Problem Behavior Checklist by parent=190.07 Problem Behavior Checklist by parent factor I (aggression)/factor 4 (hyperactivity)=65.59/24.31 Target symptoms rating by psychiatrists=5.00		
Efron	ADHD-mixed type=101(81.8%)	NR	NR
1997	ADHD-predominantly inattentive=22(17.6%)	NR	NR
Australia	ADHD-predominantly hyperactive/impulsive=2(1.6%)	125	125
	Mean IQ=98.9		
Fair			

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Dextroamphetamine vs. methylphenidate IR		
Arnold 1978 Huestis 1975 Fair	Mean changes on (p=NS for all): Conners' school behavior checklist by teachers: -21.26 vs -17.97 Sum of first 6 items on Davids' Hyperkinetic Rating Scale by teacher: -6.65 vs -5.89 Item 7 (poor schoolwork) on Davids' Hyperkinetic Rating Scale by teachers: -0.69 vs -0.79 First six items on Davids' Hyperkinetic Rating Scale by parents: -5.45 vs -5.35 Problem checklist by parents: -43.1 vs -37.79 Psychiatrists' ratings of parent-assessed target symptoms: -1.87 vs -1.62	Mean side effects reported by parents on checklist (1=not at all; 4=very much)
Efron 1997 Australia Fair	% subjects rated by their parents as improved overall compared with their usual selves: 86 (68.8%) vs 90 (72%); p=NS (CTRS-R and CPRS-R data generally corroborated with these proportions of global response to the two stimulants)	Side Effects Rating Scale (SERS)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Dextroamphetamine vs. methylphenidate IR	
Arnold 1978	p=NS on all
Huestis 1975	Poor appetite: -0.45 vs 0.35
	Awake at night: 0.07 vs -0.03
Fair	Headaches: -0.27 vs -0.27
	Tummyaches: -0.41 vs -0.31
	Side effects of drug: 0.25 vs 0.25
	Mean change in weight (kg): -1.32 vs -0.92; p=NS
Efron	Trouble sleeping: 88(70%) vs 79(64%), p=NS
1997	Poor appetite: 74(59%) vs 69(56%), p=NS
Australia	Irritable: 102(82%) vs 100(80%), p=NS
	Proneness to crying: 95(76% vs 89(71%), p=NS
Fair	Anxiousness: 85(68%) vs 76(61%), p=NS
	Sadness/unhappiness: 74(59%) vs 69(56%), p=NS
	Headaches: 38(30%) vs 30(24%), p=NS
	Stomachaches: 50(40%) vs 40(32%), p=NS
	Nightmares: 35(28%) vs 26(21%), p=NS
	Daydreams: 78(62%) vs 77(62%), p=NS
	Talking little with others: 37(30%) vs 35(28%), p=NS
	Uninterested in others: 43(34%) vs 39(31%), p=NS
	Drowsiness: 23(18%) vs 22(18%), p=NS
	Biting fingernails: 50(405) vs 56(45%), p=NS
	Unusually happy: 33(26%) vs 35(28%), p=NS
	Dizziness: 18(14%) vs 15(12%), p=NS
	Tics or nervous movements: 32(26%) vs 35(28%), p=NS
	Severity: dexamphetamine > methylphenidate on trouble sleeping, irritability, prone to crying, anxiousness, sadness/unhappiness, nightmares (data nr)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Dextroamphetamine vs. methylphenidate IR		
Arnold 1978	NR	
Huestis 1975	NR	
Fair		
Efron 1997 Australia	Total withdrawals nr Withdrawals due to advese events: 2(1.6%) vs 2(1.6%)	
Fair		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Efron 1998 Australia Fair	RCT with crossover Single center	Age between 5 and 15 years; meet DSM-IV criteria for ADHD. The DuPaul ADHD rating scale was used; each DSM-IV ADHD symptom was marked on a 4-point scale: "never or rarely," (0); "sometimes," (1); "often," (2); and "very often," (3). Only symptoms rated 2 or 3 were considered present and counted toward the diagnosis; T-score of at least 1.5 standard deviations (SD) above the mean on the Attention Problems scale of the Child Behavior Checklist or Teacher Report Form. No history of intellectual disability, gross neurologic abnormality, or Tourette's syndrome. Decision made to trial stimulant medication on clinical grounds.	NR
Elia 1990 United States Fair	RCT with crossover Single center	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, schoool, or hospital). A score 2 SD or more above age norms was required on Factor IV (hyperactivity) of the revised 39-item Conners Teacher Rating Scale(CTRS). WISC-R Full scale IQ score of 80 or more	Comorbid conduct disorder: 7 (22.6%) Comorbid oppositional disorder: 6 (19.4%) Comorbid specific developmental disorders: 9 (29%)
Elia 1991 Schmidt 1994 United States Fair	RCT with crossover Single center	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, schoool, or hospital). A score 2 SD or more above age norms was required on Factor IV (hyperactivity) of the revised 39-item Conners Teacher Rating Scale(CTRS). Parents also completed the 48-item Conners Parent Questionnaire (CPQ).	Comorbid conduct disorder: 10 (20.8%) Comorbid oppositional disorder: 12 (25%) Comorbid specific developmental disorders: 11 (22.9%) Comorbid dysthymic disorder: 1 (2%)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Efron 1998 Australia Fair	Dextroamphetamine 0.15mg/kg Methylphenidate 0.3 mg/kg Both rounded off to the nearest capsule size x 2 weeks then crossover
Elia 1990 United States Fair	Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg 3 weeks then crossover Twice daily at 9 am and 1 pm
Elia 1991 Schmidt 1994 United States Fair	Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg 3 weeks then crossover Twice daily at 9 am and 1 pm

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Efron 1998 Australia Fair	24-hour washout	NR	Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III), 28-item Conners' Teacher Rating Scale-Revised (CTRS-R), 48-item Conners' Parent Rating Scale-Revised (CPRS-R), Continuous Performance Test (CPT), Child Behavior Checklist (CBCL) Study subjects/parents were also asked to rate how they felt whilst taking each medication, compared to their usual self, at the completion of each cycle using a dichotomised 5-point scale (Nonresponse='worse than usual', 'much worse than usual' or about the same as usual'; Response='better than usual' or 'much better than usual' Children also asked to rate "How helpful was the medication?' on a 5-point scale, from 'very helpful to 'not at all helpful'	Mean age= 9.3 years 91.2% male Race nr
Elia 1990 United States Fair	≥ 3 weeks washout	NR	CTRS CPRS CGI CPT	Mean age=8.5 years 100% male Race nr
Elia 1991 Schmidt 1994 United States Fair	NR	NR	ABTRS CTRS CPRS CPQ CGI C-GAS CPT Palwin Truncal motor activity monitor	Mean age=8.6 years 100% male

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Efron	ADHD-Mixed type=84(82.4%)	NR	NR
1998	ADHD-predominantly inattentive=17(16.7%)	NR	NR
Australia	ADHD-predominantly hyperactive/impulsive=1(1%)	102	102
	Mean IQ=98.8		
Fair	Learning disability for reading=30(27.3%)		
	Learning disorder for spelling=36(32.7%)		
Elia	Mean Full Scale WISC-R IQ=102	NR	NR
1990	Mean CTRS factor I (conduct)/factor IV (hyperactivity):	NR	NR
United States	1.3/2.6	31	NR
	Mean CPRS factor I (conduct)/factor IV (hyperactivity):		
Fair	1.6/2.4		
	Stimulant naïve: 18 (37.5%)		
Elia 1991	Mean Full Scale WISC-R IQ=105.6	NR	NR
Schmidt 1994	Mean CTRS factor I (conduct) - teacher/parent rating:	NR	NR
United States	1.3/1.5	48	NR
	Mean CTRS factor IV (hyperactivity) - teacher/parent rating:		
Fair	2.6/2.4		
	Stimulant naïve: 18 (37.5%)		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Efron 1998 Australia Fair	Dextroamphetamine versus methylphenidate: Child's rating: "When I took this medication I felt:" (cases/%) Much worse than usual: 6/5.9 vs 5/4.9 Worse than usual: 13/12.9 vs 8/7.8 About the same as usual: 26/25.7 vs 25/24.5 Better than usual: 23/22.8 vs 35/34.3 Much better than usual: 33/32.7 vs 29/28.4 Child's rating: "How helpful was the medication?" (cases/%) Very helpful: 39/38.6 vs 46/45.1 A bit helpful: 25/24.8 vs 29/28.4 Not sure: 27/26.7 vs 15/14.7 Not very helpful: 5/5 vs 4/3.9 Not at all helpful: 5/5 vs 8/7.8	SERS
Elia 1990 United States Fair	dextroamphetamine=methylphenidate on all measures (limited data provided in graph format) Estimated from graphs (dextroamphetamine vs methylphenidate) <u>Mean changes in (all p=NS):</u> CGI: +2.5 vs +2.8 CPT (# correct): +9 vs +10 CTRS Factor I: -0.4 vs -0.4; CTRS Factor IV: -0.8 vs -0.8 CPRS Factor I: -0.7 vs -0.6; CPRS Factor IV: -1.2 vs -1	STESS CPRS
Elia 1991 Schmidt 1994 United States Fair	dextroamphetamine=methylphenidate on all measures (limited data provided in graph format) Estimated from graphs (dextroamphetamine vs methylphenidate) <u>Mean changes in (all p=NS):</u> CGI: 2.3 vs 2.4; GAS: 5 vs 6 39-item Conners Factor I (conduct): -0.41 vs -0.41 48-item Conners Factor I (conduct): -0.5 vs -0.39 CPT (# omission errors): -11 vs -11 39-item Conners Factor IV (hyperactivity): -0.9 vs -1 48-item Conners Factor IV (hyperactivity): -1.2 vs -1.0 CPT (# commission errors): -13 vs -14	STESS CPRS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Efron 1998 Australia Fair	NR
Elia 1990 United States Fair	NR
Elia 1991 Schmidt 1994 United States Fair	dextroamphetamine vs methylphenidate (% patients with mild/moderate/severe severity scores on STESS) (all p=NS) Decreased appetite (n=48): 40/42/13 vs 40/35/10 Sleep difficulties (n=48): 31/40/10 vs 40/31/8 Overly meticulous (n=33): 18/12/6 vs 30/3/0 Not happy (n=48): 25/33/4 vs 27/35/6 dextroamphetamine vs methylphenidate (% patients with mild/moderate/severe severity scores on CPRS) (p=NS) Nervous habits and mannerisms: 35/9/0 vs 26/21/3

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Efron 1998 Australia Fair	NR NR	
Elia 1990 United States Fair	NR NR	
Elia 1991 Schmidt 1994 United States Fair	NR NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Casellanos	RCT with crossover	(1) DSM-III-R criteria for Tourette's disorder with tics confirmed by a knowledgeable clinician	Conduct disorder=1(5%)
1997	Single center	at least 1 year prior to referral (Tourette Syndrome Classification Study Group, 1993); (2)	Oppositional defiant disorder=6(30%)
United States		symptoms of ADHD present in at least two settings; (3) Conners hyperactivity factor scores	Reading disorder=1(5%)
		from their home teacher were at least 2 SD greater than age norms	Overanxious disorder=1(5%)
Subgroup of Elia 1991		Tourette's syndrome	Obsessive-compulsive disorder=2(10%)
			Enuresis=4(20%)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Casellanos 1997 United States Subgroup of Elia 1991	Group 1 (n=12), Low-medium-high Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg Placebo Group 2 (n=6), Low-medium-medium Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 25 mg/15, 30, and 30 mg Methylphenidate 25, 40 and 40 mg/30, 50 and 50 mg Placebo Group 3 (n=4), Low-high-high Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 40, and 40 mg/15, 45, and 45 mg Methylphenidate 25, 70 and 70 mg/30, 90 and 900 mg Placebo 3 weeks then crossover Twice daily at 9 am and 1 pm Individualized curriculum and instruction provided from 9 am to 12:30 pm in a highly structured classroom. This included a positive reinforcement management program using play money. Children were paid for appropriate behavior and fined for inappropriate behavior.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Casellanos 1997 United States Subgroup of Elia 1991	≥ 4 weeks washout	Haloperidol	CTRS Historical and Examiner's Ratings from the Unified Rating Scale provided by the Tourette Syndrome Association (modified from Yale Global Tic Severity Scale)	Mean age=9.4 Gender nr 80% white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Casellanos	WISC-R Full Scale IQ=98.8	NR	# withdrawn: Group
1997	WISC-R Verbal=102	NR	1=2(9.1%), Group 2=nr,
United States	WISC-R Performance=95.6	Enrolled: Group	Group 3=n4/lost to fu
	Yale Global Tic Severity Scale (0-104)=37.3	1=22, Group	nr/Analyzed: Group
Subgroup of Elia 1991	CTRS Conduct/Hyperactivity factors=0.59/1.98	2=6, Group 3=4	1=20, Group 2=nr,
	C-GAS=42.6		Group 3=nr

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Casellanos	Tic severity	NR
1997	Dextroamphetamine had greater severity than placebo (+25%), p<0.05	
United States	Methylphenidate severity indistinguishable from placebo (-4%), p=NS	

Subgroup of Elia 1991

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Casellanos	# cases with dextroamphetamine vs methylphenidate (denominate unclear)
1997	Marked appetite suppression with transient weight loss: 4 vs 3
United States	Initial insomnia: 10 vs 2
	Transient obsessive-compulsive symptoms: 1 vs 5
Subgroup of Elia 1991	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Casellanos 1997 United States Subgroup of Elia 1991	NR NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Elia 1993 United States Fair	RCT with crossover Single center	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, schoool, or hospital). A score 2 SD or more above age norms was required on Factor IV (hyperactivity) of the CTQ-R. A WISC-R full scale IQ score > 80.	Comorbid conduct disorder: 6 (18.2%) Comorbid oppositional disorder: 7 (21.2%) Comorbid developmental disorders: 9 (27.3%)
Kauffman 1981 Fair	RCT with crossover Single center	Children diagnosed as "hyperactive," according to a set of predetermined clinical criteria	NR
Gross 1976 Poor	RCT with crossover Single center	Diagnosis of having Minimal Brain Dysfunction or Hyperkinetic Syndrome, based largely on the criteria of Clements and Peters, and showing a majority of the following traits: restlessness, hyperactivity or excessive daydreaming, short attention span, distractibility, labile emotionality or temper tantrums, overreaction to stimuli, lack of appropriate cautiousness or fear	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Elia 1993 United States Fair	Weeks 1, 2, and 3 for children < 30 kg/ > 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg Placebo 3 weeks then crossover Twice daily at 9 am and 1 pm Individualized curriculum and instruction provided from 9 am to 12:30 pm in a *highly structured classroom* . This included a positive reinforcement management program using play money. Children were paid for appropriate behavior and fined for inappropriate behavior.
Kauffman 1981 Fair	Dextroamphetamine 10-60 mg Methylphenidate 5-30 mg Placebo Twice daily: morning and noon 6 weeks, then crossover
Gross 1976 Poor	Age group 3-4/5-6/7-8/9-11/12-14: Dextroamphetamine: 2.5/4.5/7.25/10/11.25 mg Methylphenidate: 4.5/10/15/20/22.5 mg 1 week, then crossover AM and noon

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Elia 1993 United States Fair	≥ 3 weeks washout	NR	Specific Skill Series Reading (Barnell Loft, Ltd) Developing Key Concepts in Math (Barnell Loft, Ltd)ABTRS CTQ-R CGI C-GAS Rosvold's A-X Continuous Performance Task	Mean age= 9.3 years Gender NR
Kauffman 1981 Fair	NR	NR	Urine sample Returned capsules were recorded	Mean age nr 100% male 100% white
Gross 1976 Poor	None	NR	Parents asked to rate each week in terms of improvements in target symptoms and get similar ratings from the child's teacher(s): =2=much worse, -1=slightly worse, 0=no really significant change, +1=slightly improved, +2=definite improvement but symptoms still pronounced, +3=considerably improved, +4=excellent improvement but some symptoms still present to a significant degree, and +5=oustanding improvement with few residual symptoms	NR NR NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Elia 1993 United States Fair	Mean Full Scale WISC-R IQ=108.8 Mean CTQ-R factor I (conduct)=1.16 Mean CTQ-R factor IV (hyperactivity)=2.49 Mean CPQ-R factor I (conduct)=1.49 Mean CPQ-R factor IV (hyperactivity)=2.26	NR NR 33	NR/NR/33
Kauffman 1981 Fair	NR	NR NR 12	NR/NR/12
Gross 1976 Poor	NR	NR NR 50	2 (4%) withdrawn/lost to fu nr/analyzed: dextroamphetamine=48 vs methylphenidate=46

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Elia 1993 United States Fair	Combined Reading Scores *Percent correct* Dextroamphetamine vs placebo=89.5 vs 86.1; p<0.01 Methylphenidate vs placebo=89.7 vs 86.1; p<0.01 *Mean number of attempts* Dextroamphetamine vs placebo=11.4 vs 9.5; p<0.01 Methylphenidate vs placebo=10.6 vs 9.5; p<0.01 Dextroamphetamine vs methylphenidate: p<0.05 Combined Arithmetic Scores *Percent correct* Dextroamphetamine vs placebo=97.1 vs 94.0; p<0.05 Methylphenidate vs placebo=96.2 vs 94.0; p=NS *Mean number of attempts* Dextroamphetamine vs placebo=38.3 vs 30.5; p<0.01 Methylphenidate vs placebo=39.2 vs 30.5; p<0.05	STESS
Kauffman 1981 Fair	% patients with positive urinalysis: 60 vs 67; p=NS % of patient-weeks with missed doses recorded: 18 vs 13; p=NS	Side effects checklist (not specified)
Gross 1976 Poor	Average improvement: 2.3 vs 2.2; p=NS	Use of same 8-point scale used for efficacy (-2=much worse to +5=outstanding improvement)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Elia 1993 United States Fair	% patients (dextroamphetamine vs methylphenidate) Decreased appetite: 43 vs 46 Difficult with sleeping: 42 vs 36 Overly meticulous behavior: 24 and 21 Seemed unhappy: 12 vs 24 Transient tics or other nervous mannerisms: 36 vs 39
Kauffman 1981 Fair	Anorexia (incidence/patient-week): 0.32 vs 0.26; both significantly different from placebo Insomnia (incidence/patient-week): 0.20 vs 0.36; only methylphenidate significantly different from placebo Mean change in weight (kg): -0.86 vs +0.11; significant difference bewteen active drugs (p nr) Mean change in height (cm): +0.4 vs +0.4; neither significantly different from placebo
Gross 1976 Poor	Average improvement in average side effects: 0.4 vs 0.5; p=NS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Elia 1993 United States Fair	Withdrawals due to adverse events: 0 vs 0	
Kauffman 1981 Fair	NR NR	
Gross 1976 Poor	2 (4%) NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Borcherding 1990 Poor	RCT with crossover Single center	DSM-III diagnosis of Attention Deficit Disorder with Hyperactivity (ADDH); medically healthy; WISC-R full scale IQ score > 80; score 2 SDs or above their age norms on Factor 4 (hyperactivity) of the CTRS	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Borcherding 1990 Poor	Mean dosages for weeks 1/2/3: Dexmethylphenidate 0.2/0.5/0.7 mg/kg Methylphenidate 0.5/0.8/1.3 mg /kg 3 weeks then crossover Twice daily: 9 a.m. and 1 p.m.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Borcherding 1990 Poor	3-week washout	NR	Efficacy nr	Mean age=8.6 years 100% male 71.7% white, 2.2% black, 6.5% hispanic/asiatic

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Borcherding	WISC-R Full Scale IQ=106.1	NR	1 (2.2%) withdrawn/lost
1990	Mean CTRS for Factor 4 (hyperactivity)/Factor 1 (conduct):	NR	to fu nr/# analyzed
	2.5/1.2	46	ranged by outcome
Poor	28.3% stimulant naïve		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Borcherding 1990 Poor	Efficacy nr	STESS (rated by physician/child's parents) + 4 items (orofacial, stereotypic, other tics, tremor) 3 items from CPRS (nervous habits/mannerisms, compulsive actis, obsessive thinking) 20-item Leyton Obsessinal Inventory Other observations by teachers, nurses, and other professional staff, and from families (as cued by professional staff)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Borcherding 1990 Poor	Abnormal movements Abnormal movements "NOTED": 34/45 (76%) overall Abnormal movements "OBSERVED": 27/34 (79%) Of those n=27 subjects (Dextroamphetamine vs methylphenidate; p=NS on all): Abnormal movements: 6 (22%) vs 10 (37%) Orofacial movements: 7 (27.9%) vs 7 (27.9%) Steretypies: 2 (7.4%) vs 4 (14.8%) Compulsive behaviors Overall: 23/45 (51.1%) Of those 23 subjects (Dextroamphetamine vs methylphenidate; p=NS on all): Compulsive behaviors: 13 (56%) vs 5 (22%); p=0.09 STESS items (mean scores) Does things over & over a certain number of times before they seem quite right (n=38): 0.4 vs 0.4; both > placebo Meticulous; pays close attention to detail: 0.4 vs 0.3; both > placebo Overly neat and clean: 0.2 vs 0.1: only dextroamphetamine > placebo Has trouble making up his mind: 0.4 vs 0.5; methylphenidate > placebo Jerks/twitches or unusual movements: 0.2 vs 0.2; both = placebo CPRS items (mean scores) (all "both > placebo) Compulaive acts: 1.7 vs 1.5 Nervous habits & mannerisms: 1.8 vs 1.7 Obsessive thinking: 2.0 vs 2.0

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Borcherding 1990 Poor	1 (2.2%) withdrawals withdrawals due to adverse events nr	Compares results of this 100% female trial to trial of 45 boys (Castellanos 1996)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Sharp 1999 Fair	RCT with crossover Single center	Girls with ADHD symptoms present in at least 2 settings; Conners Hyperactivity factor scores from their home teacher were at least 2 SD greater than age and sex norms	NR
Simpson 1980 United States Fair	DB RCT crossover design Setting: regular elementary classrooms	Boys aged 6-12, for whom 1) hyperactivity that had been long term; 2) complaints of hyperactivity were voiced by both the parents and teachers; 3) each child had at least average intellectual abilities as measured by the WISC-R. Subjects were evaluated for hyperactivity on the basis of a physical exam, classroom observations, and through the completion of teacher, parent, and self-ratings. Medical evaluation was designed to rule out overt brain damage or CNS trauma, cerebral palsy, convulsive diosrders, CNS infection, genetic syndromes, metabolic disorders, or other medical conditions incongruous with developmental hyperactivity.	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Sharp 1999 Fair	Mean doses for weeks 1, 2, and 3: Dextroamphetamine 0.23, 0.43, and 0.64 mg/kg Methylphenidate 0.45, 0.85 and 1.28 mg/kg Twice daily: breakfast and lunch 3 weeks, then crossover
Simpson 1980 United States Fair	MPH, D-amphetamine, placebo for 8 weeks each

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Sharp 1999 Fair	3-week washout	All subjects attended accredited NIMH school 5 days a week for 3 months (academic instruction in the morning and recreation therapy activities in the afternoon)	WISC-RR, Woodcock-Johnson Achievement Battery, Conners Hyperactivity and Conduct factors, CBCL, TRF, C-GAS, CGI-SI, CPT	n=42 (includes 10 girls from another, unpublished pilot trial of sustained release dextroamphetamine vs adderall) Mean age=8.9 100% female 67% white, 19% black, 14% latina
Simpson 1980 United States Fair	NR/NR	NR	Each subject was observed daily in his classroom setting for 16 minutes via a modified form of the Direct Observation System. Reliability data was taken by an independent observer simultaneously observing and recording the subjects.	Age 6-12, mean age NR 100% male Ethnicity NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Sharp 1999 Fair	n=42 (includes 10 girls from another, unpublished pilot trial of sustained release dextroamphetamine vs adderall) SES: 48 WISC-R Full Scale IQ=105.2 WISC-R Verbal IQ=105.6 WISC-R Performance IQ=104.0 WJ Reading/Math standard scores: 95.6/96.6 C-GAS=44.6 CGI-SI=5 Teacher/Parent Conners: Hyperactivity=2.0/2.5; Conduct=0.9/1.4 CBCL: Attention problems=76.0, Externalizing behaviors=70.7, Internalizing behaviors=63.6, Total behaviors=71.0 TRF: Attention problems=70.3, Externalizing behaviors=69.7, Internalizing behaviors=61.0, Total behavior problems=69.3	150/NR/32	1 (3.1%) withdrawn/lost to fu nr/analyzed=32
Simpson 1980 United States Fair	NR	NR/NR/12	NR/NR/12

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Sharp 1999 Fair	% patients with CGI--GI ratings of "very much improved" or "much improved": 85% vs 83%; p=NS	NR
Simpson 1980 United States Fair	Results reported only for each individual child, post-hoc analysis reported to indicate that *where a positive effect was seen* , dextroamphetamine was superior to methylphenidate - but these data are not presented.	Blood count, platelet count, and urinalysis were obtained at beginning and end of each treatment phase. Height, weight, pulse, and blood pressure were recorded at each clinic visit. Urinalysis was conducted at weekly visits to determine compliance. A symptom checklist was completed during each visit to evaluate side effects.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Sharp 1999 Fair	Mean change in body weight (kg) Dextroamphetamine: -1.1; p=0.01 from baseline Methylphenidate: -0.4; p=NS from baseline
Simpson 1980 United States Fair	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Sharp 1999 Fair	1 (3.1%) total withdrawals Withdrawals due to adverse events nr	Meta-analysis of this 100% female trial
Simpson 1980 United States Fair	0 withdrawals; 0 withdrawals due to adverse events	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Adderall			
Barkley 2000 Poor	RCT with crossover Single center	DSM-IV criteria for ADHD	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Adderall	
Barkley 2000 Poor	Adderall 10 mg and 20 mg Methylphenidate 10 mg and 20 mg Placebo 1 week, then crossover Twice daily: morning and noon

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Adderall				
Barkley 2000 Poor	NR	NR	ADHD/ODD Rating Scale, Conners CPT, Stroop Word-Color Association Test, CGI	n=35 Mean age=14 85.7% male Race nr

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Adderall			
Barkley 2000 Poor	Mean IQ=103.9	NR NR 46	8 (17.4%) withdrawals/lost to fu NR/31 (89%) analyzed for parent/teen ratings; 13 (37%) analyzed from language arts teacher ratings; 15 (43%) analyzed from math teacher ratings; 33 (94%) analyzed from lab measures

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Adderall		
Barkley 2000	Mean scores for Adderall 5 mg/10 mg vs methylphenidate 5 mg/10 mg vs placebo: Parent ratings	SERS
Poor	ADHD Total: 21.3/19.0 vs 21.01/16.8 vs 21.9 ODD Total: 10.0/8.2 vs 9.7/8.2 vs 9.4 Teen self-ratings ODD Total: 6.0/5.8 vs 5.6/5.2 vs 5.1 English Teacher ADHD Total: 21.9/18.1 vs 17.9/21.5 vs 22.5 ODD Total: 4.3/3.9 vs 5.2/5.0 vs 5.1 Math Teacher ADHD Total: 17.5/16.4 vs 12.2/14.0 vs 17.7 ODD Total: 4.7/6.1 vs 3.3/3.9 vs 4.8 In-clinic tests Stroop Word Score: 46.5/48.7 vs 46.3/49.5 vs 47.1 Stroop Color Score: 44.5/47.7 vs 45.2/46.2 vs 44.3 Stroop Interference: 52.0/54.8 vs 51.8/53.2 vs 49.7 CPT Omissions: 7.1/15.0 vs 15.5/23.2 vs 14.0 CPT Commissions: 15.2/13.8 vs 16.5/15.2 vs 15.7 CPT Reaction Time (ms): 391.0/408.1 vs 388.3/396.3 vs 417.2	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Adderall	
Barkley 2000	Mean scores for Adderall 5 mg/10 mg vs methylphenidate 5 mg/10 mg vs placebo:
Poor	Parent ratings Side effects number: 4.8/5.1 vs 5.4/5.5 vs 5.1 Side effects severity: 3.1/2.8 vs 3.0/2.9 vs 2.9 Teen self-ratings Side effects number: 4.7/4.7 vs 4.3/4.8 vs 4.6 Side effects severity: 2.5/2.4 vs 3.3/2.9 vs 2.7; "...teens rated the 10 mg dose of Adderall condition as producing significantly less severe side effects than the 5 mg dose of methylphenidate" English Teacher (n=13) 2.9/3.1 vs 3.2/3.6 vs 3.8 3.3/1.9 vs 3.4/2.7 vs 1.9 Math Teacher Side Effects Number: 3.1/3.9 vs 1.9/3.1 vs 3.2 Side Effects Severity: 2.6/2.3 vs 1.5/2.4 vs 2.2

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Adderall		
Barkley 2000	NR NR	

Poor

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Pelham 1999a Fair	RCT with daily crossover Summer Treatment Program (STP) at the State University of New York at Buffalo	DSM-IV diagnosis of ADHD	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Pelham 1999a Fair	MPH=methylphenidate 1) placebo at 7:30 am, 11:30 am, and 3:30 pm 2) 0.3 mg/kg of MPH at 7:30 am, 11:30 am, and 3:30 pm 3) 0.3 mg/kg of MPH at 7:30 am and 11:30 am with 0.15 mg/kg at 3:30 pm 4) 0.3 mg/kg of MPH at 7:30 am only 5) 0.3 mg/kg of Adderall at 7:30 am and at 3:30 pm 6) 0.3 mg/kg of Adderall at 7:30 am with 0.15 mg/kg received at 3:30 pm 7) 0.3 mg/kg of Adderall at 7:30 am only Medication received Monday through Thursday throughout a period of 6 weeks for a 24-day clinical medication assessment; resulting in ~3 days of data in each of the active drug conditions and 6 days in the placebo condition

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Pelham 1999a Fair	First 2 weeks of the program served as a period of baseline observation (unclear if run-in/washout used)	Concurrent behavioral point system	Point system Classroom measures (% of points kept, percentage of assigned seatwork completed, percentage correct of seatwork, behavioral observations during seatwork period) Daily Report Cards (% of behavioral targets met) Counselor and Teacher Ratings (Inattention/Overactivity and Oppositional/Defiant subscales of the IOWA Conners Rating Scale; Pittsburgh Side Effect Rating Scale Parent Ratings: IOWA Conners Rating Scale	Mean age=10.3 90.5% male Race nr

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Pelham 1999a Fair	87% with previous use of stimulant medication 9 (43.8%) with learning problems 14 (66.7%) with comorbid oppositional defiant disorder 5 (23.8%) with comorbid conduct disorder Mean IQ=109.9 Reading achievement standard score=99.1 Math achievement standard score=105.7 ADHD items endorsed in parent structured interview: Inattention (out of 9 items)=6.1, Hyperactivity/impulsivity (out of 9 items)=5.5 oppositional/defiant items endorsed in parent structured interview=4.3 Conduct disorder items endorsed in parent structured interview=2.8 Abbreviated Conners rating scale parent=20.5 Abbreviated Conners rating scale teacher=18.2 IOWA Conners teacher rating scale inattention-overactivity/oppositional-defiant: 9.6/7.5 Disruptive behavior disorders parent rating scale: Inattention=2.2, Hyperactivity/impulsivity=2.0, Oppositional/defiant=1.8, Conduct disorder=0.4 Disruptive behavior disorders teacher rating scale: Inattention=1.7, Hyperactivity/impulsivity=1.7, Oppositional/defiant=1.6	NR/NR/21	NR/NR/NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Pelham 1999a Fair	Adderall qAM vs MPH bid vs MPH qAM b = p<0.05 vs MPH bid; c = p<0.05 vs MPH qAM <u>Counselor measures</u> Following activity/rules: 73.1c vs 70.6 vs 65.7b Noncompliance: 1.2 vs 0.8 vs 1.2 Interruption: 4.0 vs 5.3 vs 6.9 Complaining: 3.0 vs 3.0 vs 5.8b Positive peer behaviors: 5.5 vs 5.2 vs 6.4 Conduct problems: 1.7 vs 0.9 vs 0.6 Negative verbalizations: 3.6 vs 3.9 vs 6.6 IOWA Conners IQ: 3.0c vs 3.3c vs 4.3 IOWA Conners OD: 1.9c vs 2.2c vs 3.1 <u>Classroom measures:</u> Seatwork rules: 92.7 vs 91.9 vs 84.6 Peer tutoring rules: 93.9 vs 93.6 vs 90.1 Computer rules: 92.3 vs 93.4 vs 89.3 Seatwork complete: 90.2 vs 86.1 vs 86.9 Seatwork correct: 90.9 vs 89.8 vs 87.5 On-task behavior: 97.1 vs 96.1 vs 94.9 Disruptive behavior: 1.9 vs 2.5 vs 3.5 Teacher IOWA Conners IO: 0.8c vs 0.9 vs 2.0b Teacher IOWA Conners OD: 0.7 vs 0.4 vs 1.4b Daily Report Card: 82.8c vs 80.5 vs 69.0	Frequency with which raters endorsed any side effect as either moderate or severe on at least 1 day

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Pelham 1999a Fair	% children rated by Counselor/Parent/Teacher as diplaying side effects at a moderate-severe leve on at least one day: MPH qAM vs MPH 0.3/0.3/0.15 vs MPH 0.3/0.3/0.3 vs Adderall qAM vs Adderall 0.3/-/0.15 vs Adderall 0.3/-/0.3 Tics: 5/10/5 vs 5/10/0 vs 5/10/5 vs 5/5/0 vs 5/0/5 vs 5/0/5 vs 0/5/0 Appetite loss: 5/25/- vs 57/20/0 vs 33/33/- vs 29/33/- vs 71/15/- vs 62/29/- vs 52/29/- Sleep trouble (only parent ratings): 25 vs 15 vs 20 vs 20 vs 24 vs 38 vs 33

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 1999a	NR NR	

Fair

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Pelham 1999b Fair	RCT with daily crossover Summer Treatment Program (STP) through the psychology department State University of New York at Buffalo	DSM-IV diagnosis of ADHD	NR
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Pelham 1999b Fair	Adderall 7.5 mg at 7:45 am and 12.5 mg at 12:15 pm Methylphenidate 10 mg at 7:45 am and 17.5 mg at 12:15 pm Medication received Monday through Thursday throughout a period of 6 weeks for a 24-day clinical medication assessment; resulting in ~5 days of data in each of the active drug conditions and 6 days in the placebo condition
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Pelham 1999b Fair	First 2 weeks of the program served as a period of baseline observation (unclear if run-in/washout used)	NR	Point system Classroom measures (% of points kept, percentage of assigned seatwork completed, percentage correct of seatwork, behavioral observations during seatwork period) Daily Report Cards (% of behavioral targets met) Recess Rule violations (rated ~4.5 hours after ingestion of morning dose) Counselor and Teacher Ratings (Inattention/Overactivity and Oppositional/Defiant subscales of the IOWA Conners Rating Scale; Pittsburgh Side Effect Rating Scale Parent Ratings: IOWA Conners Rating Scale	Mean age=9.6 84% male 88% white
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	See Pelham 1999a	Parent affect: Positive and Negative Affect Schedule (PANAS) - comprised of two 10-item subscales (PA=positive affect, NA=negative affect) Pleasantness, successfulness, and effectiveness ratings: Parents completed a series of questions using a 7-point Likert scale (0=very pleasant/successful/effective to 6=very unpleasant/unsuccesful/ineffective)	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Pelham 1999b Fair	13 (52%) with comorbid oppositional defiant disorder 8 (32%) with comorbid conduct disorder WISC vocabulary scaled score=12.3 WISC block design scaled score=11.2 WIAT spelling scaled score=95.7 WIAT math scaled score=105.7 DSM ADHD items-parent=10.8 DSM ODD items-parent=5.3 DSM CD-parent=1.8 Abbreviated Conners-parent=22.6 Abbreviated Conners-teacher=19.6 Iowa Conners I/O-teacher=11.8 Iowa Conners O/D-teacher=9.6 Disruptive behavior disorders parent/teacher rating scale: ADHD=1.5/2.4 Oppositional/defiant=1.7/2.5 Conduct disorder=1.8/nr	NR/NR/25	NR/NR/NR
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Pelham 1999b Fair	Adderall 7.5/12.5 vs Methylphenidate 10 mg/17.5 mg; results of ANOVA of methylphenidate vs adderall; p-value: Classroom variables Rule-following Seatwork: 89.7/90.7 vs 84.3/87.8, 4.06, p=NS Peer tutoring: 95.1/95.0 vs 91.4/94.8, 3.71, p=NS Computer: 91.1/94.4 vs 87.3/92.6, 2.80, p=NS Seatwork completion: 71.6/67.1 vs 69.5/69.2, 0.00, p=NS Seatwork accuracy: 87.6/87.3 vs 87.9/87.1, 0.00, p=NS Observational measures On-task behavior: 89.0/89.9 vs 89.2/89.6, 0.00, p=NS Disruptive behavior: 6.4/6.4 vs 6.9/6.2, 0.15; p=NS Daily report card: 83.8/82.8 vs 76.4/81.7, 6.63, p<0.05 Recess rule violations: 1.0/0.4 vs 1.3/0.7, 3.21, p=NS Counselor ratings I/O: 2.4/2.2 vs 3.4/2.6, 1.4, p<0.001; O/D: 1.0/0.8 vs 2.3/1.1, 13.85, p<0.01 Teacher ratings I/O: 1.2/1.2 vs 1.8/1.1, 0.72, p=NS; O/D: 0.7/0.4 vs 1.3/0.6, 3.22, p=NS 5:00-6:00 parent ratings I/O: 0.9/0.5 vs 1.5/1.0, 5.25, p<0.05; O/D: 0.8/0.6 vs 1.2/1.1, 4.09, p=NS All evening parent ratings I/O: 1.5/1.4 vs 2.6/1.7, 3.33, p=NS; O/D: 1.9/1.2 vs 2.4/1.2, 12.17, p<0.01 Point system measures Following rules: 75.4/79.9 vs 71.4/74.5, 10.38, p=NS Attention: 68.2/68.2 vs 64.0/64.3, 5.47, p=NS Noncompliance: 0.9/1.2 vs 2.2/0.8, 5.65; p=NS Interruption: 6.2/6.8 vs 10.6/6.7, 7.48, p=0.025 Complaining/whining: 2.9/2.0 vs 4.1/2.6, 4.12, p=NS Positive peer behaviors: 8.1/7.8 vs 8.8/8.8, 1.82, p=NS Conduct problems: 0.4/0.2 vs 1.4/0.1, 5.17, p=NS Negative verbalizations: 2.0/2.2 vs 6.1/2.2, 7.89, p=0.01	Frequency with which raters endorsed any side effect as either moderate or severe on at least 1 day
Chronis 2003 (same as Pelham 1999a) Fair	1) Placebo/Placebo/Placebo 2) MPH .3/.3/.3 3) MPH .3/.3/.15 4) MPH .3/Placebo/Placebo 5) Adderall .3/Placebo/.3 6) Adderall .3/Placebo/.15 7) Adderall .3/Placebo/Placebo All p-values reflect comparison to condition #1 (Placebo/Placebo/Placebo) Positive affect (all p=NS): 1) 28.1; 2) 30.81; 3) 29.17; 4) 29.40; 5) 30.28; 6) 30.29; 7) 29.62 Negative affect (all p=NS): 1) 12.51; 2) 11.43; 3) 12.67; 4) 12.22; 5) 11.90, 6) 11.68, 7) 11.79 Parent task completion (all p=NS): 1) 2.34; 2) 1.94; 3) 2.18; 4) 2.29; 5) 2.25; 6) 1.95; 7) 2.37 Child task completion: 1) 2.46; 2) 1.61, **p<0.01**; 3) 2.47; 4) 2.17; 5) 1.78; 6) 1.77, **p<0.01**; 7) 2.17 Overall effectiveness: 1) 2.52; 2) 1.90, **p<0.01**; 3) 2.27; 4) 2.19; 5) 2.07; 6) 1.75, **p<0.001**; 7) 2.22 Pleasantness of interaction: 1) 2.76; 2) 1.65, **p<0.01**; 3) 2.41; 4) 2.26, **p<0.01**; 5) 1.67, **p<0.01**; 6) 1.44, **p<0.001**; 7) 1.98, **p<0.01**	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Pelham 1999b Fair	% children rated by Counselor/Parent as diplaying side effects at a moderate-severe leve on at least one day: Adderall 7.5 mg vs Adderall 12.5 mg vs methylphenidate 10 mg vs methylphenidate 17.5 mg Motor Tics Counselors: 8 vs 8 vs 8 vs 4 Parents: 4 vs 8 vs 4 vs 0 Trouble sleeping Counselors: n/a Parents: 48 vs 64 vs 32 vs 24 Loss of appetite Counselors: 76 vs 80 vs 60 vs 68 Parents: 40 vs 72 vs 8 vs 20
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 1999b Fair	1 (4%) withdrawal due to exacerbation of pre-existing motor tics	
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Pliszka 2000 Faraone 2001 Fair	RCT Parallel	DISC criteria for ADHD; ≥ 1.5 SD above the mean for his/her age and sex on the IOWA CTRS Inattention/Overactivity (I/O) factor; parent Conners Global Index score similarly elevated	NR
Manos 1999 Poor	CCT (Adderall and methylphenidate protocols run simultaneously) Crossover Pediatric Assessment and Evaluation Service (PAES) of a large, urban teaching hospital	DSM-IV criteria for ADHD; presence of at least 6 symptoms of inattention and/or at least 6 symptoms of hyperactivity/impulsivity; symptoms significantly interfered with functioning at home and at school as noted during structured (Computerized Diagnostic Interview Schedule for Children) or semistructured clinical interviews; symptom severity on broad-band (Conners ASQ) and narrow-band (ARS) rating scales was at threshold or above (i.e., rated 2 or 3); multiple raters agreed to the presence of the symptoms; empirical comparison to norms indicated at least a 1.5 SD cutoff on at least one rating scale	Oppositional defiant disorder=21.4%

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Pliszka 2000	Adderall
Faraone 2001	< 60 kg = 5-15 mg > 60 kg = 10-30 mg
Fair	Week1: single am dose Week2: morning dose doubled if no improvement on morning+afternoon or just afternoon teacher ratings; after school dose added if morning+afternoon teacher ratings improved, but parent rating remained impaired Week3: noon dose added if afternoon behavior remained impaired; after school dose added if evening behavior had not been impaired in week 1 but now was Methylphenidate < 60 kg = 5-25 mg > 60 kg = 10-50 mg Week1: single am dose Week2: morning dose doubled if no improvement on morning+afternoon (teacher); noon dose added if no afternoon improvement (teacher); after school dose added if evening rating (parent) remained impaired; morning dose doubled and a noon dose added if morning+afternoon teacher ratings Week3: noon dose doubled if the afternoon ratings (teacher) remained impaired 3 weeks; Flexible dosing and timing
Manos 1999	Adderall (once daily) vs methylphenidate (twice daily) 1-week for each condition
Poor	Fixed dosage: 4 conditions: (1) placebo; (2) 5 mg; (3) 10 mg; (4) 15 mg Six dose orders were used such that the highest dose (15 mg) was given only when preceded by the moderate dose (10 mg) Dose orders were assigned in a random fashion Parents blind to dosage

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Pliszka 2000 Faraone 2001 Fair	NR/NR	NR	IOWA CTRS, Conners Global Index, CGI	Mean age=8.2 Gender nr Race nr
Manos 1999 Poor			ARS, Conners ASQ, SSQ-R	Mean age=10.1 78.6% male 92.8% white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Pliszka 2000 Faraone 2001 Fair	IOWA CTRS I/O: 2.2 IOWA CTRS A/D: 1.4 Conners Global: 2.1 ODD=62% CD=10.3% Anxiety disorder=12.1% RCMAS: 15.8% CDI: 12.2% Weight (kg): 33.3	73 screened/eligible unclear/enrolled 58	5 (8.6%) withdrawn/0 lost to fu/58 analyzed Adderall n=20 Methylphenidate n=20 Placebo n=18
Manos 1999 Poor	Inattentive type=45.2% Combined type=54.8% Mood disorder=1.2% Anxiety disorder=4.8% Learning disability=47.6%	Referred=60/eligible=NR/participated=159	MPH n=42 (matched by "hand-selecting" by age, diagnostic category and gender to Adderall group), Adderall n=42

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Pliszka 2000 Faraone 2001 Fair	Adderall vs methylphenidate IOWA CTRS I/O: AM: 0.44 vs 0.78; p=NS PM: 0.54 vs 0.85, p=NS Average: 0.49 vs 0.81, p<0.05 IOWA CTRS A/D AM: 0.25 vs 0.47, p=NS PM: 0.33 vs 0.51, p=NS Average: 0.29 vs 0.49, p<0.05 Conners Global Index: 1.04 vs 1.28, p=NS CGI Improvement: 1.6 vs 2.35, p<0.05 Responders %: 90 vs 65 Final weight (kg): 37 vs 33.2, p=NS Dosing regimen: 70% of Adderall subjects required only an AM dose vs 85% in the methylphenidate group received 2 or more doses per day; p=0.003	Multi-Modality Treatment of ADHD; parents asked to rate severity (none, mild, moderate, severe) of facial tics, tongue movements, picking at skin, anxious, tired, headache, stomach ache, irritable, sad or tearful, appetite loss, and "gets wild when medication wears off"
Manos 1999 Poor	"Best dose" comparisons of Adderall vs methylphenidate <u>Parent ratings (no significant differences, but p-values nr)</u> ASQ: 49.83 vs 50.64 ARS: 11.79 vs 10.10 Composite ratings: 3.50 vs 3.31 <u>Teacher ratings (no significant differences, but p-values nr)</u> ASQ: 51.47 vs 56.12 SSQ-R, total: 1.67 vs 1.92 SSQ-R, part: 2.23 vs 2.68	SE/BMS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Pliszka 2000	All p=NS
Faraone 2001	
	Facial tics: 1 (5%) vs 0
Fair	Tongue movements: 1 (5%) vs 0
	Picking at skin: 1 (5%) vs 0
	Anxious: 1 (5%) vs 2 (10%)
	Tired: 2 (10%) vs 4 (20%)
	Headache: 2 (10%) vs 0
	Stomach ache: 5 (25%) vs 1 (5%)
	Irritable: 5 (25%) 3 (15%)
	Sad, tearful: 5 (25%) vs 3 (15%)
	Appetite loss: 3 (15%) vs 3 (15%)
	Gets wild when medication wears off: 7 (35%) vs 8 (40%)
Manos	Results described as "no differences", but p-values nr
1999	Insomnia: 5 (11.9%) vs 2 (4.8%)
	Decreased appetite: 0 vs 1(2.4%)
Poor	Tics/nervousness: 0 vs 0

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Pliszka 2000	Total withdrawals=5 (8.6%)	
Faraone 2001	Withdrawals due to adverse events: 2 (10%) vs 1 (5%), p=NS	
Fair		
Manos 1999	NR NR	
Poor		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
McCracken 2003 United States	RCT Crossover Multicenter (4 academic sites)	Potential subjects were screened to meet the following eligibility criteria: age 6 to 12 years; diagnosis of DSM-IV ADHD (combined or hyperactive-impulsive subtype as determined by a comprehensive clinician evaluation and selected modules of the Diagnostic Interview Schedule for Children, Version IV-Lifetime [DISC-IV]) administered by a research staff member with suitable training; no evidence of mental retardation; and history of positive response to psychostimulant medication, or no prior stimulant treatment. Information pertaining to co-occurring psychopathology from the clinical evaluation was supplemented by the Comorbid Disorders Checklist, a parent-report questionnaire composed of DSM-III-R symptom items. All diagnoses were based on DSM-IV criteria. Subjects were excluded if they met criteria for any of the following: comorbid psychiatric conditions including psychosis, pervasive developmental disorder, bipolar disorder; severe obsessive-compulsive disorder, severe depressive or anxiety disorder (severe defined as any comorbid disorder with impairment necessitating concurrent treatment of any type); a clinically significant medical cor hypertension, abnormal laboratory test result); need for ongoing medical treatment; intoleranc to psychostimulants; history of nonresponse to Adderall; or history of a tic disorder.	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
McCracken 2003 United States	SLI381 (Adderall XR) 10, 20, or 30mg, placebo, or active control (Adderall 10mg) Mean Dose: NR Subjects who tolerated initial exposure to SLI381 were randomly assigned in crossover design to each of five treatment weeks: SLI381 10mg, SLI381 20mg, SLI381 30mg, Adderall 10mg, and placebo, each administered daily at 7:30 AM

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
McCracken 2003 United States	1 week washout period with discontinuation of previous stimulant medication	NR	Primary Outcome Measure: the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) scale Attention and Deportment variables as completed by the classroom raters Other Measures: Permanent Product Measure of Performance (PERMP), Parent Global Assessment global behavior rating scale	Mean age= 9.5 yrs (SD 1.9) 86.3% male 49% white 15.7% black 23.5% Hispanic 5.9% Asian/Pacific Islander 5.9% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
McCracken 2003 United States	ADHD diagnosis: Hyperactive-impulsive=2% Combined=98% Duration of prior stimulant treatment: mean=1.7 yrs (SD 1.7) ADHD treatment before study entry: amphetamine only=33.3% methylphenidate only=58.8% none listed=7.8%	Number screened NR/51 eligible/51 enrolled	2 of 51 withdrawn because of withdrawal of consent; 49 rondomized for crossover treatment 2 of 47 withdrawn (1 stomachache, 1 developed an excusion criterion) 45 completed 5 weeks of doubleblind portion of study (all treatment conditions) 3 withdrew in extra or "makeup" week ITT=49

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
McCracken 2003 United States	**p-values for active drug vs placebo:** **Adderall XR 30mg/20mg/10mg/Adderall 10mg** **SKAMP Attention (hours post-dose)** 1.5-hr: 0.0015/0.0513/0.5846/0.0025 4.5-hr: <0.0001/0.0023/0.0269/0.0005 6.0-hr: <0.0001/<0.0001/0.0003/0.0005 7.5-hr: <0.0001/<0.0001/0.0001/0.0002 9.0-hr: 0.0001/0.0072/0.2442/0.8264 10.5-hr: <0.0001/<0.0001/0.0062/0.3250 12.0-hr: 0.0034/0.0077/0.0626/0.3064 **SKAMP Deportment (hours post-dose)** 1.5-hr: 0.0002/0.0031/0.0725/<0.0001 4.5-hr: <0.0001/<0.0001/0.0090/<0.0001 6.0-hr: <0.0001/<0.0001/<0.0001/<0.0001 7.5-hr: <0.0001/<0.0001/0.0083/0.0004 10.5-hr: <0.0001/0.0021/0.0724/0.0246 12.0-hr: 0.0062/0.0531/0.9878/0.7901 **PERMP no. attempted (hours post-dose)** 1.5-hr: 0.0030/0.0283/0.0920/0.0004 4.5-hr: <0.0001/0.0006/0.0136/0.0850 6.0-hr: <0.0001/<0.0001/0.0001/0.0015 7.5-hr: <0.0001/<0.0001/0.0017/0.0157 9.0-hr: <0.0001/0.0001/0.0230/0.0048 10.5-hr: <0.0001/<0.0001/0.0101/0.7626/ 12.0-hr: 0.0017/0.0053/0.9938/0.7508 **PERMP no. correct (hours post-dose)** 1.5-hr: 0.0059/0.0333/0.1121/0.0007 4.5-hr: <0.0001/<0.0001/0.0020/0.0353 6.0-hr: <0.0001/<0.0001/<0.0001/0.0007 7.5-hr: <0.0001/<0.0001/0.0029/0.0667 9.0-hr: <0.0001/<0.0001/0.0128/0.0195 10.5-hr: <0.0001/<0.0001/0.0025/0.3424 12.0-hr: 0.0001/0.0007/0.5420/0.9304	Parents completed weekly Side Effect Rating Scale; teachers completed Teacher Side Effect Rating scale each analog classroom day; adverse events were noted by study physicians or research staff

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
McCracken 2003 United States	Study medications well tolerated overall. No serious side effects reported or observed. Only anorexia displayed a dose-dependent pattern of increases for Adderall XR doses. Placebo (n=49) vs. Adderall 10mg (n=48) vs. SLI381 10mg(n=48) vs. SLI381 20mg (n=50) vs. SLI381 30mg (n=49) Nervousness: 29 (59.2%) vs. 22 (45.8%), 26 (54.2%) vs. 28 (56.0%) vs. 21 (42.9%) Insomnia: 10 (20.4%) vs. 17 (35.4%) vs. 6 (12.5%) vs. 16 (32.0%) vs. 14 (28.6%) Anxiety: 10 (20.4%) vs. 11 (22.9%) vs. 13 (27.1%) vs. 11 (22%) vs. 9 (18.4%) Emotional lability: 5 (10.2%) vs. 10 (20.8%) vs. 13 (27.1%) vs. 9 (18%) vs. 6 (12.2%) Depression: 5 (10.2%) vs. 4 (8.3%) vs. 5 (10.4%) vs 11 (22.0%) vs. 3 (6.1%) Abdominal pain: 12 (24.5%) vs. 16 (33.3%) vs. 14 (29.2%) vs 18 (36.0%) vs. 17 (34.7%) Headache: 12 (24.5%) vs. 12 (25.0%) vs. 12 (25.0%) vs. 15 (30.0%) vs. 12 (24.5%) Anorexia: 11 (22.4%) vs. 22 (45.8%) vs. 13 (27.1%) vs. 20 (40.0%) vs. 27 (55.1%)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
McCracken 2003 United States	Of the 49 randomized subjects, 3 withdrew due to AE's	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
IR vs. SR formulations of methylphenidate			
Bergman 1991 United States Poor	CCT Crossover Setting NR	DSM-III diagnosis of Attention Deficit Disorder with Hyperactivity (ADDH)	11 (26.2%) met criteria for reading disability (ADHD/RD) based on Reading Quotient index which calculated by dividing the Wide Range Achievement Test-Revised (WRAT-R) Reading test score by the WISC-R Full Scale IQ score. If the resulting RQ score was less than 0.85, indicating a discrepancy of more than 1 SD between reading and IQ scores, the subject was categorized as reading disabled (ADHD/RD)
Fitzpatrick 1992 Poor quality	Study design unclear (CCT or RCT?) Crossover Setting NR	Diagnosis of ADD in the Diagnostic Instrument for Childhood and Adolescence (DICA)	63.1% oppositional disorder

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
IR vs. SR formulations of methylphenidate	
Bergman 1991 United States Poor	Sustained-release methylphenidate 20 mg (single morning dose) Short-acting (regular) methylphenidate 10 mg (twice daily - morning and afternoon) Placebo 1 day
Fitzpatrick 1992 Poor quality	Per-protocol dosages for patients < 30 kg / > 30 kg / mean dosages: Placebo Sustained-release (SR) methylphenidate 20 mg am / 20 mg am / mean=20 mg Standard (SA) methylphenidate: 7.5 mg in am and pm / 10 mg in am and pm / mean=17.1 mg Combination SA + SR methylphenidate: 5 mg SA+20 mg SR in am and 5 mg SA in pm / 7.5 SA + 20 mg SR in am and 7.5 mg SA in pm / mean=20 mg SR + 11.8 mg SA Each phase lasted 2 weeks

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
IR vs. SR formulations of methylphenidate				
Bergman 1991 United States Poor	NR/NR	NR	Identical Pairs version of the CPT (CPT-IP)	Mean age nr (between 6 and 12) 100% male Ethnicity nr
Fitzpatrick 1992 Poor quality	NR/NR	NR	Conners Hyperactivity Index; IOWA Inattention/Overactivity and Aggression/Noncompliance Scales; Hyperactivity, Attention, and Aggression Subscales of Time on Task Scale (TOT); parents and teachers answered open-ended questions about child's behavior, academics, relations with others, concentration, and attitude toward school and responses rated by blinded rater as +1=positive, 0=blank/irrelevant/neutral, -1=negative responses; Continuous Performance Test (CPT) - administered 1 and 3 hours after each dose (target=2 identical numbers); Paired-associate learning (PAL) test	Mean age=8.71 89.5% male Race nr

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
IR vs. SR formulations of methylphenidate			
Bergman 1991 United States Poor	NR	NR/NR/42	NR/NR/NR
Fitzpatrick 1992 Poor quality	Weight=31.45 kg Wechsler Scale IQ=114.11 Peabody Individual Achievement Scale=105.68 Conners Hyperactivity Index-Parent/Teacher: 1.79/1.74 IOWA Inattention-Overactivity-Parent/Teacher=2.01/2.09 IOWA Aggression/Noncompliance-Parent/Teacher: 1.27/1.18 TOTS Aggression-Parent/Teacher: 0.88/0.72 TOTS Hyperactivity-Parent/Teacher=0.86/0.56 TOTS Attention Parent/Teacher=0.32/0.46	NR/NR/19	NR/NR/NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
IR vs. SR formulations of methylphenidate		
Bergman 1991 United States Poor	SR methylphenidate = short-acting methylphenidate on all measures (data nr)	NR
Fitzpatrick 1992 Poor quality	SR vs SA vs Combination (SR+SA) p=NS for all <u>All outcomes reported for Parent/Teacher</u> Conners: 0.98/0.77 vs 0.96/0.73 vs 0.81/0.58 Inattention-Overactivity: 0.98/0.92 vs 1.01/0.87 vs 0.79/0.70 Noncompliance: 0.84/0.43 vs 0.80/0.48 vs 0.62/0.25 Aggression: 0.68/0.31 vs 0.56/0.24 vs 0.60/0.26 Hyperactivity: 0.22/-0.12 vs 0.20/-0.16 vs 0.18/-0.29 Attention: 0.72/0.88 vs 0.81/1.01 vs 0.91/1.05 Comments valence: -0.05/0.20 vs 0.17/0.19 vs 0.18/0.40 <u>Other ratings</u>: Parent ranks: 2.16 vs 2.18 vs 1.87 Laboratory rating: 0.13 vs 0.13 vs 0.09 Weight (kg): 31.59 vs 31.41 vs 31.33	Parents interviewed concerning 12 side effects relevant to stimulant therapy and a side effect was counted if it was prevalent to a marked extent during the latter part of the 2-week period

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
IR vs. SR formulations of methylphenidate	
Bergman 1991 United States Poor	NR
Fitzpatrick 1992 Poor quality	Percentage of patients with side effects: SR vs SA vs Combination, p=NS for all Sleep problem: 36.8 vs 42.1 vs 63.2 Appetite decrease: 36.8 vs 15.8 vs 26.3 Crying: 21.0 vs 15.8 vs 26.3 Sadness: 0.0 vs 10.5 vs 0.0 Unhappiness: 21.0 vs 5.3 vs 15.8 Anger: 31.6 vs 10.5 vs 26.3 Headaches: 10.5 vs 10.5 vs 5.3 Increased thirst: 5.3 vs 0 vs 0 Dry mouth: 0 vs 0 vs 0 Nausea: 0 vs 5.3 vs 0 Stomachaches: 0 vs 5.3 vs 0 Shakiness: 0 vs 0 vs 5.3

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
IR vs. SR formulations of methylphenidate		
Bergman 1991 United States Poor	NR NR	
Fitzpatrick 1992 Poor quality	NR NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Pelham 1987 Poor	RCT Crossover Summer Treatment Program	ADD with or without hyperactivity based on a structured parental interview (not described); teacher ratings on the Swanson, Nolan and Pelham rating scale comprised of DSM-III symptoms; ACTRS and IOWA CTRS scales derived from teacher ratings of the CTRS	4 (30.8%) with Conduct Disorder 6 (46.1%) with Oppositional Defiant Disorder 3 (23.1%) with Learning Disability

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Pelham	Placebo (twice daily)
1987	Methylphenidate 20 mg (twice daily)
	Sustained release methylphenidate 20 mg (once daily)
Poor	
	Condition varied daily and 5 to 9 days of data were gathered per medication condition

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Pelham 1987 Poor	NR/NR	NR	Daily Frequencies=frequencies with which numerous appropriate and inappropriate behaviors occurred daily Time out=average number of time outs per day Classroom measures=rates of on-task behavior and rul-following behavior; 2-minute, timed arithmetic drill, 10-minute, timed reading task (number attempted and percentage correct) Rating scales: Teacher ratings on ACTRS; counselor ratings on Revised Behavior Problems Checklist (35 items rated on a 7-point scale with lower ratings equalling positive evaluations) Daily Report Card=Percentage of days that the child reached daily report criterion Observed Peer Interaction=Percentages of time that children were engaged in positive, negative, or no interactions with their peers were recorded using a modification of the RECESS code	Mean age=8.8 100% male Race NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Pelham	WISC-R IQ=95.3	NR/NR/13	NR/NR/NR
1987	ACRS Parent/Teacher=17.7/19.0		
	IOWA CTRS		
Poor	Inattention/Overactivity=11.9		
	Aggression=8.9		
	Woodcock-Johnson Achievement Test		
	Reading=91.6		
	Mathematics=97.0		
	Language=91.4		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Pelham 1987 Poor	Methylphenidate vs sustained release methylphenidate, t-test, p-value: Daily frequencies Following rules: 3.5 vs 4.3, t=1.8, p=NS Noncompliance: 3.4 vs 4.3, t=-2.5, p<0.05 Positive peer behaviors=100.2 vs 95.8, t=0.8, p=NS Conduct problems: 0.3 vs 0.4, t=-0.4, p=NS Negative verbalizations=3.4 vs 4.8, t=-2.3, p<0.05 N. of time outs/day: 0.5 vs 0.7, t=-1.2, p=NS Classroom % on task=95.2 vs 96.5, t=-0.6, p=NS % on following rules=93.9 vs 92.2, t=0.6, p=NS Timed math No. attempted=21.0 vs 21.7, t=-0.5, p=NS % correct=9.3 4 vs 94.4, t=-0.5, p=NS Timed reading No. attempted=19.8 vs 18.2, t=1.4, p=NS % correct=79.8 vs 77.9, t=0.4, p=NS Seatwork % completion=86.1 vs 89.1, t=-0.9, p=NS % correct=83.7 vs 82.9, t=0.3, p=NS Teacher rating: 1.9 vs 3.4, t=-1.3, p=NS Counselor rating: 106.4 vs 105.9, t=0.1, p=NS Positive daily report card (% of days received): 83.2 vs 81.8, t=0.2, p=NS Observed interactions Positive peer: 97.9 vs 95.2, t=1.6, p=NS Negative peer: 1.4 vs 1.5, t=-0.2, p=NS No interactions: 0.7 vs 3.3, t=-1.8, p=NS	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Pelham 1987	Evidence of anorexia: Standard methylphenidate=4 (30.8%) vs 5 (38.5%); p=NS

Poor

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 1987	NR NR	

Poor

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Pelham 2001 Fair	RCT, DB, crossover Setting: regular home and school settings Sunday-Friday; study site for Saturday laboratory sessions from 6:45 AM to 8:15 PM	Children between the ages of 6 and 12 with a DSM-IV diagnosis of ADHD (any subtype). Children met DSM diagnostic criteria using a rule in which a symptom was defined as present if either parents or teachers endorsed it, with overlap between raters on at least 1 symptom. Medicated with a stable dose of methylphenidate for at least 4 weeks before the beginning of the study	Oppositional defiant disorder=43% Conduct disorder=37%

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Pelham 2001 Fair	Placebo Methylphenidate immediate release, three times daily (7:30 AM, 11:30 AM, 3:30 PM), average dose=29 mg (0.88 mg/kg) Methylphenidate extended release (Concerta), once daily in the morning (7:30 AM), average dose=35 mg (1.05 mg/kg) Flexible dosing determined based on that child's MPH dosing before the study Double-dummy placebo design 7 days, then crossover

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Pelham 2001 Fair	NR/NR	4-6 sessions of behavioral parent training was provided (how to use behavioral techniques in the home setting); teacher received 1-4 clinical contacts during which a consulting teacher worked with each child's teacher to establish a daily report card (DRC) and to consult on other classroom management strategies	Primary outcome measures: (1) IOWA inattention/overactivity (I/O) in the natural setting and (2) SKAMP attention in the laboratory classroom Other dependent measures: Natural setting: (1) teacher and parent IOWA Conners ratings, (2) teacher and parent abbreviated Conners ratings, (3) teacher peer relations ratings, (4) teacher and parent global effectiveness ratings, and (5) individualized DRC percentages Laboratory classroom: 1) frequencies of rule violations, 2) math problems completed, 3) math problems percentage correct, 4) teacher SKAMP ratings, 5) observed on-task behavior, 6) observed disruptive behavior, 7) records of individualized target behaviors (DRC goals), and 8(teacher end-of-day IOWA Conners ratings Structured recreation: 1) frequencies of rule violations, 2) frequencies of negative behaviors, 30 observed disruptive behavior, 4) observed on-task behavior, 5) records of individualized target behaviors (DRC), and 6) counselor end-of-day IOWA-Conners ratings Recess: 1) frequencies of rule violations, and 2) observed disruptive behavior Daily behavior: 10 % following activity rules, 2) noncompliance, 3)	Mean age 9.1 89% male 94% white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Pelham 2001 Fair	Pre-study MPH use: BID dosing=57%; TID dosing=43% Full-scale IQ (WISC-III)=104.8 Reading achievement (WIAT)=104.1 Math achievement (WAIT)=98.8 Spelling achievement (WIAT)=96.3 DISC hyperactive/impulsive symptoms=8.3 DISC inattention symptoms endorsed=7.1 Parent SNAP ratings Inattention=2.26 Hyperactivity/impulsivity=1.96 Oppositional/defiant=1.56 Parent/DBD Ratings Inattention=2.15 Hyperactivity/impulsivity=1.83 Oppositional/defiant=1.28 Conduct disorder=0.26 Parent IOWA Conners ratings Inattention/overactivity=10.42 Oppositional/defiant=7.28 Parent abbreviated Conners rating=18.06 Teacher SNAP ratings Inattention=2.04 Hyperactivity/impulsivity=1.62 Oppositional/defiant=1.56 Teacher DBD ratings Inattention=1.82 Hyperactivity/impulsivity=1.47 Oppositional/defiant=0.75 Teacer IOWA Conners ratings Inattention/overactivity=9.65 Oppositional/defiant=4.07 Teacher abbreviated Conners rating=14.96 Teacher peer relations rating=5.33	NR/NR/70	2 (2.8%) withdrawn/lost to fu nr/analyzed 68 5 children missed one of 3 testing sessions

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Pelham 2001 Fair	Placebo / tid IR MPH / Concerta, p-value = MPH IR vs Concerta Natural setting Teacher ratings Inattention/overactivity: 10.34 vs 5 vs 4.69, p=NS; Oppositional/defiant: 5.09 vs 1.99 vs 1.81, p=NS Abbreviated Conners; 16.40 vs 7.4 vs 7.82, p=NS; Peer interactions: 4.29 vs 4.03 vs 3.41; p=NS Global effectiveness: NS on any classification Daily report card (% positive): 61.17 vs 84.36 vs 86.06 Parent ratings Inattention/overactivity: 10.59 vs 5.93 vs 4.78; p=0.05; Oppositional/defiant: 8.85 vs 5.26 vs 4.82; p=NS Abbreviated Conners: 19.91 vs 11.41 vs 9.49; p=0.05 Global effectiveness: Poor: 73.5% vs 8.8% vs 5.9%; p=NS; Fair: 22.1% vs 26.5% vs 27.9%, p=NS Good: 2.9% vs 50.0% vs 39.7%, p=NS; Excellent: 1.5% vs 14.5% vs 26.5%, p=NS (p=NS for all remaining comparisons of tid IR MPH vs Concerta) Recreational Activities -- Counselor measures Rule violations (mean #)-- 7:45-8:10: 2.52 vs 2.83 vs 2.21; 9:55-10:25: 4 vs 2.58 vs 2.70 1:25-1:55: 5.87 vs 2.17 vs 2.39; 4:35-5:00: 5.21 vs 2.84 vs 2.53 Negative behavior (mean #)-- 7:45-8:10: 1.53 vs 4.86 vs 1.73; 9:55-10:25: 3.62 vs 1.14 vs 1.14 1:25-1:55: 6.25 vs 0.98 vs 2.45; 4:35-5:00: 4.76 vs 2.83 vs 1.58 Individual target goals-- 7:45-8:10: 79.05 vs 69.01 vs 75.13; 9:55-10:25: 65.44 vs 82.30 vs 78.91 1:25-1:55: 56.13 vs 81.25 vs 74.22; 4:35-5:00: 58.82 vs 76.43 vs 80.73 Observer measure negative behavior-- 7:45-8:10: 3.24 vs 4.00 vs 4.21; 9:55-10:25: 6.99 vs 2.13 vs 2.97 1:25-1:55: 8.96 vs 2.17 vs 3.47; 4:35-5:00: 8.91 vs 4.61 vs 2.86 Recess measures (means) Rule violations-- 11:05: 0.81 vs 0.44 vs 0.36; 2:50: 1.10 vs 0.66 vs 0.52; 7:45: 2.07 vs 1.42 vs 1.53; Negative behavior-- 11:05: 10.37 vs 7.48 vs 8.56; 2:50: 14.03 vs 10.13 vs 7.65; 7:45: 13.76 vs 8.88 vs 7.73 Laboratory sessions (means) (overall daily measures) Behavior frequencies Following rules: 47.5% vs 60.2% vs 61.3%; Noncompliance: 5.76 vs 2.73 vs 2.14 Interruption: 21.6 vs 10.5 vs 10.58; Complaining/whining: 15.45 vs 6.95 vs 6.67 Positive peer behaviors: 10.52 vs 9.86 vs 9.20; conduct problems: 3.81 vs 1.53 vs 0.60 Negative verbalizations: 18.27 vs 9.29 vs 7.14 Teacher rating-- Inattention/overactivity: 5.01 vs 2.75 vs 2.59; Oppositional/defiant: 2.18 vs 1.19 vs 1.30 Abbreviated Conners: 7.03 vs 4.03 vs 3.75; Peer interactions: 0.24 vs 0.15 vs 0.15 Counselor rating-- Inattention/overactivity: 7.95 vs 6.31 vs 6.10; Oppositional/defiant: 3.63 vs 2.58 vs 2.36 Abbreviated Conners: 12.70 vs 9.91 vs 9.26; Peer interactions: 0.77 vs 0.56 vs 0.49	Spontaneous reports; parents completed questions regarding AEs, sleep quality, appetite, and tics; sleep quality for the week was rated as poor, fair, good, or excellent; food intake for the week relative to usual food intake was rated as less, usual amount, or more

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Pelham 2001	Placebo vs qd Concerta vs tid IR MPH
	Serious adverse events: 0 vs 0 vs 0
Fair	Motor tics: 0 vs 4/70 (5.7%) vs 0
	Sleep(% patients)
	Excellent: 12% vs 13% vs 7%
	Good: 57% vs 47% vs 65%
	Fair: 21% vs 24% vs 21%
	Poor: 10% vs 16% vs 7%
	Usual appetite: 59% vs 77% vs 66%
	Appetite loss: 4: vs 18% vs 24%
	Headache: 16 (23.2%) vs 8 (11.8%) vs 11 (15.9%)
	Abdominal pain: 8 (11.6%) 9 (13.2%) vs 12 (17.4%)
	Upper respiratory tract infection: 3 (4.3%) vs 2 (2.9%) vs 3 (4.3%)
	Accidental injury: 2 (2.9%) vs 1 (1.5%) vs 3 (4.3%)
	Vomiting: 2 (2.9%) vs 2 (2.9%) vs 2 (2.9%)
	Twitching: 0 vs 0 vs 4 (5.8%)
	Diarrhea: 1 (1.4%) vs 0 (0.0%) vs 2 (2.9%)
	Pharyngitis: 0 (0.0%) vs 1 (1.5%) vs 2 (2.9%)
	Rhinitis: 0 (0.0%) vs 1 (1.5%) vs 2 (2.9%)
	Dizziness: 0 (0.0%) vs 2 (2.9%) vs 1 (1.4%)
	Urinary incontinence: 2 (2.9%) vs 0 (0.0%) vs 1 (1.4%)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 2001	2 (2.8%) withdrawals overall (group assignment unclear)	
Fair	Withdrawals due to adverse events: none reported	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Cox 2004 Fair	RCT Crossover	Diagnosis of current ADHD as determined by parent-report questionnaire and structured clinical interviews (DuPaul ADHD Rating Scale-IV, Diagnostic Interview Schedule for Children, Standardized Interview for Adult ADHD; positive history of MPH responsiveness disclosed by subject and parent reports; and current daily driving activity	NR
Wolraich 2001 United States Fair	RCT Parallel Multicenter	Boys and girls, ages 6 to 12 years, with a clinical diagnosis of any subtype of ADHD; patients who were taking MPH or had taken it in the past had to have been on a total daily MPH dose (IR or IR/SR combination) of at least 10 mg but not more than 60 mg)	46.5% ODD 11.3% Conduct Disorder 5.3% Tic Disorder 1.4% Anxiety Disorder 0.7% Depression

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Cox 2004 Fair	Methylphenidate in equal doses at 8 am, noon, and 4 pm (mean = 60 mg) Methylphenidate osmotic, controlled-release oral formulation (OROS) at 8 am (mean=54 mg) 7 days of dosage maintenance
Wolraich 2001 United States Fair	Methylphenidate (MPH) mean dose=29.5 (three times daily at 7:30, 11:30 and 3:30) Methylphenidate osmotic, controlled-release, oral dosage form (OROS MPH) mean dose=34.3 (once daily at 7:30) Duration=4 weeks Patients that had not been receiving MPH during 4 weeks prior to study entry started in a 4-week open titration phase where they were ALL given OROS MPH at 18 mg QD and this was increased to 36 mg QD and then to 54 mg QD as necessary

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Cox 2004 Fair	24 hour washout	NR	Atari Research Driving Simulator Composite Score (Impaired Driving Score) consisting of Off Road, Veering Across Midline, Standard Deviation Steering, Inappropriate Braking, % Missed Stop Signals, % Bumps, and % Crashes	Mean age =17.2 100% male Race NR
Wolraich 2001 United States Fair	NR/NR	NR	1) IOWA CTRS 2) SNAP-IV (18 items that reflect ADHD symptoms in the DSM-IV and 8 items that reflect oppositional defiant disorder) 3) Children's Global Assessment Scale (C-GAS) - parent rating 4) Clinical Global Impressions-Improvement (CGI-I) - investigator rated 5) Global Assessment of Efficacy rating by parents/teachers (4-point scale of 0=poor, 1=fair, 2=good, 3=excellent) in response to question: "What is your opinion of the effectiveness of treatment this week?" 6) Peer Interaction: On day 27, teachers rated 6 items from the SNAP-IV and 1 item from the IOWA Conners Rating Scale 7) Parent Satisfaction Questionnaire: based on questionnaire used in the NIMH Multimodal Treatment Study of Children with ADHD (MTA)	Mean age=9 82.6% male 84.4% White 7.4% Black 0.4% Asian 3.5% Hispanic

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Cox 2004 Fair	Inattentive type=4(66.7%) Combined type=2(33.3%) Proportion taking medicatin for ADHD at baseline NR Mean baseline dose of MPH NR	NR/NR/7	1 (14.3%) withdrawn/0 lost to fu/analyzed=6
Wolraich 2001 United States Fair	ADHD Diagnosis 73.4% combined 19.5% inattentive 7.1% hyperactive/impulsive Previous stimulant therapy 20.2% None 6.4% Not in previous 4 weeks 5.7% Non-MPH 67.7% MPH	Screened=500/Enrolled=405/Randomized=312	Withdrawn=206 (66%)/Lost to follow-up=1(0.3%)/Analyzed=277 (MPH n=94, MPH OROS n=94, Placebo n=89)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Cox 2004 Fair	OROS Methylphenidate vs methylphenidate TID IDS 2 PM: -0.55 vs -0.54, p=NS 5 PM: -2.2 vs -1.04, p=NS 8 PM: -1.98 vs 4.23, p=0.01 11 PM: -1.65 vs 5.1, p=???? (wrote to author - reported as 0.1 in text but I think that's wrong) Individual parameters (F-value/p-value for MPH TID vs MPH OROS) Standard deviation steering: F=0.65, p=0.42 Off Road: 2.50/0.12 Veering across midling: 2.11/0.15 Inappropriate braking: 4.47/0.04 % missed stop signals: 5.76/0.02 % bumps: 1.35/0.25 % crashes: 3.13/0.08 Speeding: 1.60/0.21 Standard deviation speed: 4.19/0.04 Risky Driving Means (daily driving diaries - self reported): 2.6 vs 3.2, p=NS	NR
Wolraich 2001 United States Fair	Mean change in IOWA Conners Scores (OROS MPH vs IR MPH) (p-values NR, but narrative states there are NS differences): <u>Teacher/Parent scores:</u> Inattention/Overactivity: -3.76/-4.79 vs -3.59/-3.73 Oppositional/Defiance: -1.6/-3.24 vs -1.3/-2.36 <u>Mean changes in secondary measures of efficacy (teacher ratings)</u> Peer Interaction: -0.33 vs -0.21 SNAP-IV Inattention: -0.69 vs -0.80 SNAP-IV Hyperactivity/Impulsivity: -0.64 vs -0.69 SNAP-IV Oppositional Defiant Disorder: -0.36 vs -0.32 Global Efficacy at end of study: 1.42 vs 1.43 <u>Mean change in secondary measures of efficacy (parent ratings)</u> SNAP-IV Inattention: -0.91 vs -0.77 SNAP-IV Hyperactive/Impulsive: -0.91 vs -0.74 SNAP-IV Oppositional Defiance Disorder: -0.65 vs -0.41 Global Efficacy at end of study: 1.47 vs 1.28 <u>Investigator ratings</u> Mean CGI at end of study: 4.24 vs 4.19 % of patients on CGI rated as "much" or "very much" improved: 46.7% vs 47.2% <u>Other</u> Global assessment of efficacy, % patients teachers/parents rated as "good or excellent": 42.9%/54.0% vs 46.9%/46.5% CGI, % patients rated as "very much improved or much improved": 46.7% vs 47.2% Parent Satisfaction Questionnaire (% pleased/very pleased/extremely pleased): 62.6% vs 64%	AEs collected at days 7, 14 and 28 by asking parents whether any new developmetn in the child's health had occurred since the last clinic visit. Spontaneously reported AEs also were recorded. Sleep quality rated by parents for previous 2 weeks on days 0, 14, and 28 as Excellent, good, fair, or poor Food intake rated by parents for previous 2 weeks on days 14 and 28 as more than before, about the same amount as before, or less than before Motor and verbal tics: parents asked about presence of and/or any changes in severity or specificity on days 0, 14, and 28

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Cox 2004 Fair	NR
Wolraich 2001 United States Fair	Any adverse event: 42.3% vs 46.2%, p-value nr Sleep: no differences (data nr) Appetite (% of patients who were eating less than usual during the previous two weeks): day 14=22.5% vs 18.8%, p=NS; day 28=data nr but described as "similar" New onset tics (# patients): 0 vs 1 (1%), p=NS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Cox 2004 Fair	1 (14.3%) withdrawals 0 due to adverse events	
Wolraich 2001 United States Fair	Withdrawals due to adverse events: 1% vs 1% Total withdrawals: 15 (16%) vs 13 (13.8%)	Although the numbers enrolled vs analyzed are described in the text and in a figure, they are confusing and difficult to reconcile with each other.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Whitehouse 1980 United States Fair	RCT Parallel Double-blind Setting NR	Children of both sexes, 6-14 years of age, with a diagnosis of minimal brain dysfunction (MBD); symptoms of MBD had been satisfactorily controlled by methylphenidate 10 mg given twice daily for at least 1 month prior to study-no medication changes were made during this period; the children were outpatients attending school, in good health, taking no other chronic medications	NR
Steele 2006 Canada	RCT Open-label Parallel Multicenter	Physically healthy, male and female outpatients, aged 6 - 12 years inclusive, with a documented Diagnostic Statistical Manual-Fourth Edition (DSM-IV) diagnosis of Attention-Deficit/Hyperactivity Disorder. These criteria were confirmed by a clinical and structured interview (the Kiddie-Schedule for Affective Disorders and Schizophrenia -Present and Lifetime Version, K-SADS-PL, version 1.0). Subjects were medication naïve or currently on ADHD medication therapy; had a baseline Clinical Global Impression-Severity (CGI-S) score of 4 or greater (at least “moderate” severity); and had to demonstrate significant after-school/evening behavioural difficulties as assessed by the clinician via parent/child interviews. To approximate clinical practice settings, psychotropic medications to treat non-ADHD disorders and psychological interventions were permitted as long as the treatment/intervention had been stable for a minimum of 4 weeks prior to entry and did not change nor newly commence during the trial. Exclusion criteria included: known MPH non-responders, hypersensitivity, or adversely affected by methylphenidate; concomitant use of cc	Oppositional Defiant Disorder: 43.1%, 38.4% Conduct Disorder: 1.4%, 0 Anxiety disorder: 5.5%, 2.7%

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Whitehouse 1980 United States Fair	Standard methylphenidate 20 mg (twice daily) Sustained-release methylphenidate 20 mg (once daily) Duration=2 weeks Dosing schedule: 30 minutes prior to breakfast; 30 minutes before lunch
Steele 2006 Canada	OROS-MPH: Mean Dose: 37.8 mg/day (SD 11.9) Initiated on 18 mg once daily. Over 4 weeks, the subjects were titrated by weekly increases, at the investigators' discretion; to the next dose level (27 mg, then 36 mg) to a maximum of 54 mg. IR-MPH: Mean Dose: 33.3 mg/day (SD 13.2) Initiated at whatever dose the clinician felt was appropriate. Over 4 weeks each individual dose was titrated weekly by 5 mg or 10 mg increments, according to the manufacturer's recommendations and the investigator's clinical judgment, to a suggested maximum daily dose of 60 mg.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Whitehouse 1980 United States Fair	Run-in: one month of standard methylphenidate 20 mg (twice daily) prior to study/no washout	NR	Bender Visual Motor Gestalt Goodenought-Harris Drawing psychometics tests Physician questionnaire (not described) completed at visits 1 , 2 and 3 Teacher questionnaire (not described) completed within 4 days prior to the patients entering the study and again 4 days before the final visit	Mean age=8.5 83.3% male 86.7% white 13.3% black
Steele 2006 Canada	Minimum 3-day washout from stimulant or non-stimulant medication to treat ADHD	Psychotropic medications to treat non-ADHD disorders and psychological interventions permitted as long as treatment/intervention had been stable at least 4 weeks prior to entry and did not change nor newly commence during the trial	Primary Outcome Measure: parent completed 26 item Swanson, Nolan and Pelham–Fourth Edition (SNAP-IV) rating scale Other Measures: 10-item Inattention/Overactivity with Aggression (IOWA) Conners Parent Rating Scale, 27-item Conners Parent Rating Scale (short), 36-item Parent Stress Index (PSI), Physician-rated Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Improvement (CGI-I), Parent/caregiver report of satisfaction with ADHD treatment, 100 mm Visual Analog Scale (VAS) of homework and for social play ability scored by the parent/caregiver, Resource Use Questionnaire (RUQ)	Mean age=9.1 yrs (Range=6-12 yrs) 83.4% male 86.9% caucasian 3.4% black 9% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Whitehouse 1980 United States Fair	Height (inches)=50 Weight (pounds)=57.8 Right-handedness=90% Physician Questionnaire Overt Signs of Tension: 1.63 (2.00 vs 1.21; p<0.05) Teacher questionnaire Tension/Anxiety: 10.9 (10.00 vs 12.00; p<0.05)	NR/NR/34	4 (11.8%) withdrawn/0 lost to fu/30 analyzed
Steele 2006 Canada	ADHD diagnosis: predominantly inattentive=18.6% combined type=79.3% predominantly H/I=2.1%	187/NR/147	2 withdrawn (didn't receive study medication) ITT n=143 Safety analysis n=145

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Whitehouse 1980 United States Fair	Mean change scores (visit 3 compared to visit 1) for sustained release vs standard: <u>Teacher</u> Total score: -1 vs -8, p<0.05 Conduct Problem: 0 vs -3, p<0.05 Inattentive/Passive: 0 vs 0 Tension/Anxiety: -1 vs -1 Hyperactivity: 0 vs -2 Social ability: 0 vs 0 Parent/teacher questionnaire: 0 vs -1 <u>Parent Questionnaire</u> Total score: -11 vs -8 Conduct Problem: -2 vs 0; p<0.05 Anxiety: -1 vs -2 Impulsive/Hyperactive: -2 vs 0 Learning problem: 0 vs 0 Psychosomatic: -1 vs 0 Perfectionism: 0 vs 0 Antisocial: 0 vs 0 Muscular tension: -1 vs 0 Parent/Teacher Questionnaire: -2 vs -1	NR
Steele 2006 Canada	Achieved remission (SNAP-IV-18) at endpoint: 44% vs. 16%; p=0.0002 Remission rates higher in OROS-MPH group than in IR-MHP group at week 4 (33% vs, 14%; p=0.01) and at week 8 (47% vs. 16%; p=0.0003) <u>Mean change from baseline score (SD) at study endpoint (OROS-MPH vs. IR-MPH):</u> SNAP-IV 26-item (ADHD + ODD items) Scale: -25.5 (18.7) vs. -17.5 (15.2) SNAP-IV 18-item (ADHD items) Scale: -19.6 (13.9) vs. -14.3 (11.6) IOWA Conners Parent Rating Scale, Total: -9.4 (8.5) vs. -6.0 (5.9) IOWA Conners Parent Rating Scale, Inattention/Overactivity Sub-scale: -5.4 (4.5) vs. -3.9 (3.2) Conners Parent Rating Scale: -27.5 (21.9) vs. -19.2 (15.6) Parent Stress Index, Short Form: +14.0 (19.2) vs. +6.1 (14.8) Visual analog scale (mm): homework: -31.8 (29.6) vs. -23.0 (33.8) Visual analog scale (mm): social play: -17.9 (30.4) vs. -7.5 (27.0) CGI-I: mean rating (SD): 2.0 (1.2) vs. 2.6 (1.4); p=0.0008 CGI-S: mean change from baseline rating (SD): -2.2 (1.2) vs. -1.6 (1.4); p=0.0005 Parent satisfaction with current ADHD medication: mean rating (SD): 4.0 (1.3) vs. 3.4 (1.3); p=0.003	Safety assessments collected included adverse events, physical examination, vital signs, and body weight

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Whitehouse 1980 United States Fair	Adverse reactions: 5 (31.3%) vs 2 (14.3%), p=NS (consisted of headache, hyperactivity and restlessness)
Steele 2006 Canada	Adverse events were reported for 82% of subjects in both groups. No serious adverse events were reported. Any event: 82% vs. 82% Any possibly medication related event: 64% vs. 52% Decreased appetite: 24% vs. 32% Headache: 19% vs. 16% Insomnia: 17% vs. 14% Abdominal pain: 14% vs. 12% Nervousness: 13% vs. 12% Emotional lability: 13% vs. 3% Agitation: 11% vs. 7% Fatigue: 10% vs. 3% Flu-like symptoms: 10% vs. 10% Sleep disorder: 4% vs. 10%

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Whitehouse 1980 United States Fair	4 (11.8%) (group assignment NR) No withdrawals due to adverse events	
Steele 2006 Canada	Total =24 (16.6%) AEs=8 (5.5%)	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Findling 2006 Australia, Canada, United States	RCT Double-blind Parallel Multicenter	Children aged 6–12 years were eligible to participate if they met diagnostic criteria for one of the three subtypes of ADHD as described in the Diagnostic & Statistical Manual of Mental Disorders, 4th Edition and had been on a stable dose of MPH for at least 3 weeks prior to screening. The diagnosis of ADHD was confirmed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children— Present and Lifetime version (K-SADS-PL). Inclusion Criteria: Male and female children aged 6–12 years (inclusive); On a stable dose of methylphenidate ≥3 weeks prior to screening; diagnosed with ADHD based on DSM-IV criteria for any subtype and confirmed by administration of the K-SADS-PL interview at screening; attending a school setting in which a single teacher could make morning and afternoon assessments of the child's behavior. Exclusion criteria: Female who had experienced menarche; co-morbid psychiatric disorder requiring medication; history of seizure, tic disorder, or a family history of Tourette's disorder; IQ test score below 80, or functioning at a level of intelligence indicative of an IQ below 80; the use of unapproved medi	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Findling 2006 Australia, Canada, United States	Mean Dose: NR MPH-IR twice-daily (morning and lunch-time), EqXL once-daily (morning) followed by placebo at lunch-time, or placebo twice-daily (morning and lunch-time) for 3 weeks. The dosages of the active treatments were determined according to the child's pre-study MPH regimen: Children on a previous total daily dose of 10–20 mg IR MPH or 20 mg ER MPH were randomized to receive either 10 mg MPH-IR twice-daily, 20 mg EqXL once-daily, or placebo; children on a previous total daily dose of 25–40 mg IR MPH or >20 mg to £40 mg ER MPH were randomized to receive 20 mg MPH-IR twice-daily, 40 mg EqXL once-daily, or placebo; and children on a previous total daily dose >40 mg IR MPH or >40 mg ER MPH were randomized to receive 30 mg MPH-IR twice-daily, 60 mg EqXL once-daily or placebo.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Findling 2006 Australia, Canada, United States	NR	NR	Primary Outcome Measure: the inattention/ overactivity (I/O) component of the overall Teacher's IOWA Conners' Questionnaire obtained from the SNAP-IV questionnaire Other Measures: IOWA Conners' Rating Scale, the 40-item SNAP-IV (which includes the IOWA Conners' Rating scale as a subscale), the Clinical Global Impression (CGI) Scale and the CGI Improvement scale, the Parent's Global Assessment (PGA)	Mean age=9.5 yrs (Range=6-12 yrs) 79.2% male 85.8% caucasian 5.3% Afro-Carribean 0.3% Asian 1.6% Hispanic 6.9% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Findling 2006 Australia, Canada, United States	ADHD Subtype: Inattention: 23% Hyperactive/Impulsivity: 5.7% Combined subtype: 71.4%	346/NR/327 318 received treatment	9 withdrawn due to failure to meet all eligibility criteria 318 analyzed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Findling 2006 Australia, Canada, United States	Difference from placebo (95% CI) for MPH-IR vs EqXL Teacher's Ratings: I/O component of 10-item IOWA Conners' Rating Scale 1-week: -2.4 (-3.36, -1.39) vs -1.9 (-2.87, -0.91) 2-week: -2.6 (-3.70, -1.43) vs. -2.4 (-3.58, -1.31) 3-week: -3.4 (-4.53, -2.26) vs. -3.1 (-4.26, -2.00) Teacher's Ratings: O/D component of 10-item IOWA Conners' Rating Scale 1-week: -1.7 (-2.54, -0.38) vs. -1.5 (-2.32, -0.62) 2-week: -1.9 (-2.81, -0.93) vs. -1.8 (-2.69, -0.81) 3-week: -2.4 (-3.36, -1.38) vs. -2.5 (-3.47, -1.48) Parent's Ratings: I/O component of 10-item IOWA Conners' Rating Scale 1-week: -2.3 (-3.31, -1.22) vs. -1.3 (-2.33, -0.23) 2-week: -2.6 (-3.65, -1.53) vs. -1.9 (-2.97, -0.86) 3-week: -3.0 (-4.09, -1.85) vs. -1.7 (-2.78, -0.54) Parent's Ratings: O/D component of 10-item IOWA Conners' Rating Scale 1-week: -2.1 (-3.22, -1.04) vs. -1.8 (-2.89, -0.71) 2-week: -2.5 (-3.64, -1.30) vs. -2.1 (-3.26, -0.92) 3-week: -2.3 (-3.46, -1.16) vs. -1.6 (-2.74, -0.44)	Throughout study, safety assessments were performed including hematology measures, biochemistry tests, urinalysis, weight, vital signs, and physical examination. Reported AE's were recorded giving duration, intensity and relationship to study drug, action taken, outcome, and seriousness. In addition, parents and teachers completed the Barkley Side Effects Rating Scale on smae days as respective SNAP-IV ratings

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Findling 2006 Australia, Canada, United States	Adverse events occurring in ≥ 3% of patients [placebo (n=46) vs. MPH-IR (n=133) vs. EqXL (n=139)]: Headache: 4.3% vs. 13.5% vs. 18.0% (p=0.059) Anorexia: 0 vs. 3.0% vs. 6.5% (p=0.131) Abdominal pain, upper: 6.5% vs. 6.8% vs. 5.8% (p=0.951) ADHD: 34.8% vs. 4.5% vs. 5.8% (p<0.001) Nasopharyngitis: 6.5% vs. 1.5% vs. 5.8% (p=0.098) Insomnia: 0 vs. 3.8% vs. 4.3% (p-0.497) Decreased appetite: 0 vs. 2.3% vs. 3.6% (p=0.564) Pyrexia: 6.5% vs. 0.8% vs. 2.9% (p=0.077) Vomiting NOS: 4.3% vs. 3.0% vs. 2.2% (p=0.657) Irritability: 2.2% vs. 3.8% vs. 1.4% (p=0.499)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Findling 2006 Australia, Canada, United States	33/318 (10.4%) withdrew before study completion 21/318 (6.6%) withdrew due to adverse events 9/327 postrandomization exclusions	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Gau 2006 Taiwan	RCT Open-label University outpatient clinic	Patients, aged 6–15, with a clinical diagnosis of any subtype of ADHD. Patients were included in this study if they were taking MPH on a total daily dose of MPH of 10 mg but not more than 40 mg for past 3 months. They were able to comply with the study visit schedules; and their mothers and teachers were willing and able to complete the weekly assessments. Patients were excluded from participation if they had significant gastrointestinal problems, a history of hypertension, known hypersensitivity to MPH, or a co-existing medical condition or concurrent medication (such as monoamine oxidase inhibitors, and medicines used to treat depression, prevent seizure, or prevent blood clots) likely to interfere with the safe administration of MPH. Patients with glaucoma, Tourette's Syndrome, an active seizure disorder, or a psychotic disorder were excluded, as were girls who had reached menarche.	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Gau 2006 Taiwan	OROS MPH Mean Dose: 27.7 mg Dose Range: 18-36 mg IR MPH Mean Dose: 26.7 mg Dose Range: 15-30 mg

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Gau 2006 Taiwan	All study subjects washed out MPH for 5-7 days	NR	Chinese version of the Conner's Teacher Rating Scale-Revised: Short Form (CTRS-R:S) Other Measures: Chinese version of the Conner's Parent Rating Scale-Revised: Short Form (CPRS-R:S), Chinese Version of the Swanson, Kotin, Agler, M-Flynn and Pelham (SKAMP) Rating Scale, Chinese version of the Social Adjustment Scale for Children and Adolescents (SAICA), Investigator Clinical Global Impression (CGI), Parent Satisfaction Questionnaire (PSQ)	Mean age=10.5 yrs (Range=6-15 yrs) 90.6% male Ethnicity: NR (study completed in Taiwan)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Gau 2006 Taiwan	ADHD diagnosis: Combined: 78.1% Inattentive: 18.8% Hyperactive: 3.1% CTRS-R:S, mean (SD): 72.6 (11.5) CPRS-R:s, mean (SD): 77.6 (9.7) SKAMP, mean (SD): 72.5 (15.5) SAICA, mean (SD): 62.6 (12.5) BSEQ, mean (SD): 24.1 (20.6) Vital signs, mean (SD): Systolic pressure : 97.2 (15.3) Diastolic pressure: 58.2 (10.9) Heart rate: 84.9 (14.8)	NR/NR/64	0/0/64

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Gau 2006 Taiwan	Connors' Teaching Rating Scale-Revised, Short Form-C, Day 13-Baseline, mean (SD) OROS vs. IR: Inattention: -1.38 (2.30) vs. -0.84 (1.97) Hyperactivity-Impulsivity: -3.16 (3.76) vs. -3.22 (4.09) Oppositional: -2.13 (2.97) vs. -1.58 (3.55) ADHD-index: -5.58 (6.38) vs. -5.97 (6.59) Connors' Teaching Rating Scale-Revised, Short Form-C, Day 27-Baseline, mean (SD) OROS vs. IR: Inattention: -1.90 (3.00) vs. -1.44 (2.12) Hyperactivity-Impulsivity: -4.94 (4.11) vs. -4.00 (5.13) Oppositional: -3.03 (3.93) vs. -1.91 (3.90) ADHD-index: -9.20 (7.36) vs. -7.13 (7.62) Conners' Parent Rating Scale-Revised: Short Form-C, Day 13-Baseline, mean (SD) OROS vs. IR: Inattention: -4.78 (5.28) vs. -4.72 (5.31) Hyperactivity-Impulsivity: -6.22 (5.13) vs. -5.25 (5.06) Oppositional: -3.69 (3.36) vs. -3.56 (3.53) ADHD-index: -9.97 (8.26) vs. -9.66 (8.23) Conners' Parent Rating Scale-Revised: Short Form-C, Day 27-Baseline, mean (SD) OROS vs. IR: Inattention: -5.63 (5.14) vs. -4.19 (4.84) Hyperactivity-Impulsivity: -7.53 (4.84) vs. -5.84 (5.01) Oppositional: -3.87 (3.32) vs. -3.41 (3.79) ADHD-index: -11.59 (7.82) vs. -9.03 (8.29) SKAMP, Day 13-Baseline mean (SD) OROS vs. IR: Attention: -1.77 (3.16) vs. -1.72 (4.08) Deportment: -2.77 (4.05) vs. -3.25 (4.13) SKAMP, Day 27-Baseline mean (SD) OROS vs. IR: Attention: -3.71 (3.39) vs. -2.98 (5.29) Deportment: -4.65 (5.53) vs. -4.41 (6.71) At final assessment, OROS group had greater proportion of subjects veing very much or much	Barkley's Side Effects Questionnaire (BSEQ) was used to measure side effects of MPH. Vital signs (including systolic BP & pulse rate) were checked and any AE was documented if any occurred at each visit.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Gau 2006 Taiwan	Percentage of side effects with increased BSEQ score from baseline, day 27, OROS vs. IR MPH: Decreased appetite: 46.9 vs. 59.4 (p=0.316) Insomnia/sleep trouble: 40.6 vs. 46.9 (p=0.614) Stomachache: 31.3 vs. 25.0 (p=0.578) Headache: 21.9 vs. 34.4 (p=0.266) Nightmares: 7.8 vs. 25.0 (0.351) Uninterested in others: 28.1 vs. 40.6 (p=0.292) Irritable: 9.4 vs. 21.9 (p=0.169) Dry mouth: 31.3 vs. 17.2 (p=0.79) Sad/unhappy, prone to crying: 31.3 vs. 43.8 (p=0.302) Anxious: 18.7 vs. 31.3 (p=0.248) Bites fingernails: 18.7 vs. 25.0 (p=0.545) Drowsiness: 7.8 vs. 18.8 (p=0.741) Tics or nervous movements: 7.8 vs. 18.8 (p=0.741) No difference in vital signs on day 28 between groups

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Gau 2006 Taiwan	0/0	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Dopfner 2004 Germany designed as a non-inferiority trial	RCT, DB, crossover Multicenter Analogue classroom setting, with each group having a trial period of 2.5 weeks; trial phase consisted of three phases: phases 1 and 2 were 4 workdays plus the weekend; and trial phase 3 was 4 workdays).	Children between 8 and 15 years who met ICD-10 diagnosis of Hyperkinetic Disorder (F90) of a DSM-IV diagnosis of ADHD using a diagnostic checklist, DCL-HKS. All patients were methylphenidate responders on the basis of clinical assessment. They also had to have an intelligence IQ≥85 and a body weight >20 kg.	44% (35 patients) had ODD or CD

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Dopfner 2004 Germany designed as a non-inferiority trial	Medikinet-Retard (methylphenidate ER) qd Methylphenidate IR (MPH IR) bid Placebo Dosage varied: 9 patients (11%) received 10 mg/d; 54 (68%) patients recevied 20 mg/d; 14 patients (17%) received 30 mg; and 2 patients (3%) received 40mg.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Dopfner 2004 Germany designed as a non-inferiority trial	1 workday run-in / No (MPH dose prior to trial had to be unchanged during the previous month)	NR	Primary efficacy: SKAMP (Swanson, Kotkin, Agler, M-Flynn, and Pelham) scores, with subscales of conduct or attention-to-rules index and the attention index; PERMP (Permanent Product Measure of Performance, an age-appropriate math test) was used for academic performance. The PERMP was assessed for number of problems attempted and number correct. SKAMP and PERMP both were assessed daily at 9:30 am, 11:30 am, 13:00 pm, 15:30 pm and 16:45 pm. Secondary measures included an ADHD rating scale (FBB-HKS) assessed at 13:00 for the mornings and 16:45 for the afternoons.	Mean age: 10.0 yrs Gender: 89.9% male Ethnicity NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Dopfner 2004 Germany designed as a non-inferiority trial	Mean IQ: 103.0 (+/- 10.4) DSM-IV diagnosis of ADHD Combined type: 92.4% Predominately inattentive: 7.6%	NR/ NR/ 82	3/ NR/ 79

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Dopfner 2004 Germany designed as a non-inferiority trial	Results of repeated measures analysis of variance of SKAMP and PERMP scores, Treatment effect: SKAMP attention: F 2.77 = 27.4, p<0.000 SKAMP deportment: F 2.77 = 18.8; p<0.000 PERMP no. attempted: F 2.77 = 17.8; p<0.000 PERMP no. correct: F 2.77 = 17.2; p<0.000	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Dopfner 2004 Germany designed as a non-inferiority trial	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Dopfner 2004 Germany designed as a non-inferiority trial	NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Extended release formulations of Methylphenidate			
Lopez 2003 Fair	RCT Crossover Simulated school setting (18 children per classroom) Single-blind (medicating nurse unblinded; but all other study personnel and patients were blinded)	Children who met ADHD criteria bsaed on the Diagnostic Interview Schedule for Children	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Extended release formulations of Methylphenidate	
Lopez 2003 Fair	Methylphenidate osmotic controlled release delivery system (MPH OROS) 18 mg or 36 mg Methylphenidate spheroidal oral drug absorption system (MPH SODAS) 20 mg Placebo 5-single dose test sessions (one practice visit, three active treatments and placebo)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Extended release formulations of Methylphenidate				
Lopez 2003 Fair	NR/NR	NR	(1) Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale (SKAMP): Attention, Deportment, and Combined Ratings subscales (2) Paper/pencil math tests: written assignments administered as four pages of 100 math problems each in ascending order of difficulty over a 10-minute period (difficulty altered for each participant's skill level); math test-attempted and math test-correct	Mean age=9.0 80.5% male 36% White 27% African American 36% Hispanic

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Extended release formulations of Methylphenidate			
Lopez 2003 Fair	NR	NR/NR/36	0 withdrawn/0 lost to fu/36 analyzed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Extended release formulations of Methylphenidate		
Lopez 2003 Fair	MPH SODAS 20mg vs MPH OROS 18mg vs MPH OROS 36mg vs Placebo; p=values reflect comparison to MPH SODAS Mean change from baseline for SKAMP-attention $AUC_{(0-4)}$: -2.48 vs -1.36 (p=0.015) vs -1.55 (p=0.043) vs 1.24 (p<0.001) $AUC_{(0-8)}$: -4.48 vs -2.72 (p=NS) vs -3.24 (p=NS) vs 3.79 (p<0.001) Greatest improvement: 54% at 2 hrs vs 35% at 1 hour vs 35% at 3 hrs Mean change from baseline for SKAMP-deportment $AUC_{(0-4)}$: -1.67 vs -0.28 (p<0.001) vs -0.55 (p=0.004) vs 0.95 (p<0.001) $AUC_{(0-8)}$: -2.81 vs -0.82 (p=0.018) vs -1.34 (p=0.078) vs 2.85 (p<0.001) Greatest improvement: 63%/2 hrs vs 32%/8 hrs vs 40%/6 hrs Mean change from baseline for SKAMP-combined $AUC_{(0-4)}$: -2.05 vs -0.78 (p<0.001) vs -1.01 (p=0.003) vs 1.09 (p<0.001) $AUC_{(0-8)}$: -3.58 vs -1.70 (p=0.01) vs -2.22 (p=0.061) vs 3.28 (p<0.001) Math test-attempted $AUC_{(0-4)}$: 112 vs 62 (p=0.066) vs 69 (p=NS) vs -39 (p<0.001) $AUC_{(0-8)}$: 202 vs 115 (p=NS) vs 137 (p=NS) vs -123 (p<0.001) Greatest improvement: 52%/2 hrs/41% at 1 hr; 26%/8 hrs Math Test Correct $AUC_{(0-4)}$: 104.07 vs 45.44 (p=0.026) vs 58.55 (p=0.080) vs -40.6 (p<0.001) $AUC_{(0-8)}$: 183 vs 100 (p=NS) vs 117 (p=NS) vs -124.7 (p<0.001) Greatest improvement: 52%/2 hrs vs 39%/1 hr vs 26%/8 hrs	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Extended release formulations of Methylphenidate	
Lopez 2003 Fair	Number (proportion) patients with at least one adverse event: 1 (2.7%) vs 1 (2.7%) vs 1 (2.7%)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Extended release formulations of Methylphenidate		
Lopez 2003 Fair	Total withdrawals=0 Withdrawals due to adverse events=0	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Swanson 2004 Sonuga-Burke 2004 United States COMACS Study	RCT, DB, crossover multicenter	Children 6-12 years old with diagnoses of a DSM-IV subtype of ADHD (inattentive type, hyperactive-impulsice type, or combined type) who were being treated with methylphenidate (MPH) 10 to 60 mg/d. Children were deeemd otherwise healthy by medical history, phsycial examination, vital sigh measurements, and by clinical laboratory assessments. Children also had to demonstrated the ability to swallow PLA study-treatment capsules whole and without difficulty.	~25% had a comorbid condition, with anxiety and ODD the most frequently reported conditions

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Swanson 2004 Sonuga-Burke 2004 United States COMACS Study	Methylphenidate extended release (Metadate CD®) vs methylphenidate extended release (Concerta®) vs placebo Dose level assigned according to preexisting MPH dose requirements: Low (≤ 20 mg): 20 mg vs 18 mg Medium (> 20 to 40 mg): 40 mg vs 36 mg High (> 40 mg): 60 mg vs 54 mg Duration 7 days

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Swanson 2004 Sonuga-Burke 2004 United States COMACS Study	No run-in or washout	NR	SKAMP Written 10-minute math test	9.6 years 73.8% male 68.9% white 11.5% black 1.7% asian 12.4% hispanic 5.4% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Swanson 2004 Sonuga-Burke 2004 United States COMACS Study	Subtype of ADHD Inattentive: 13% Hyperactive/Inattentive: 4.8% Combined: 82.1%	214 / 184 / 184	27 (14.7%) withdrawn/lost to fu NR/184 analyzed (Metadate n=174; Concerta n=181; placebo n=183)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Swanson 2004 Sonuga-Burke 2004 United States COMACS Study	Effect sizes: Metadate CD® vs Concerta® SKAMP deportment Hours post-dose 0.0: -.23 vs -.18 1.5: 0.82 vs 0.52 3.0: 0.89 vs 0.50 4.5: 0.80 vs 0.50 6.0: 0.76 vs 0.66 7.5: 0.54 vs 0.51 12: 0.06 vs 0.25 SKAMP attention 0.0: -0.59 vs -0.58 1.5: 0.70 vs 0.41 3.0: 0.72 vs 0.48 4.5: 0.66 vs 0.42 6.0: 0.65 vs 0.64 7.5: 0.50 vs 0.53 12: 0.06 vs 0.25 PERMP - # correct math problems 0.0: -0.27 vs -0.33 1.5: 0.57 vs 0.42 3.0: 0.56 vs 0.42 4.5: 0.59 vs 0.40 6.0: 0.58 vs 0.54 7.5: 0.50 vs 0.53 12: 0.10 vs 0.28	Adverse events reported by patient, parent, or guardian were characterized by an investigator as being mild (requires minimal or no treatment), moderate (result in low level inconvenience or concern) or severe (interrupt a patient's usual daily activity and may require drug or other therapy); parent or guardian completed the Barkley Side Effect Rating Scale

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Swanson 2004	Parent ratings of side effects on the Barkley Scale: no differences (data NR)
Sonuga-Burke 2004	
United States	Metadate CD® vs Concerta® vs placebo
	Gastrointestinal disorders: 4.6% vs 6.1% vs 7.1%
COMACS Study	Abdominal pain upper: 3.4% vs 4.4% vs 3.3%
	Vomiting NOS: 0.6% vs 0.6% vs 2.2%
	Infections and infestations: 0.6% vs 2.8% vs 1.1%
	Injury, poisonings, and procedural complications: 3.4% vs 1.7% vs 2.7%
	Metabolism and nutrition disorders: 4.6% vs 6.1% vs 2.2%
	Anorexia: 2.9% vs 2.8% vs 1.1%
	Appetite decreased NOS: 1.7% vs 3.3% vs 0.5%
	Nervous system disorders: 3.4% vs 5.5% vs 5.5%
	Headache NOS: 1.7% vs 3.9% vs 3.3%
	Psychiatric disorders: 6.9% vs 7.2% vs 9.3%
	Insomnia: 1.7% vs 1.7% vs 3.3%
	Irritability: 1.7% vs 1.1% vs 2.7%

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Swanson 2004	Total withdrawals: NR	
Sonuga-Burke 2004	Withdrawals due to adverse events: 0	
United States	vs 0.5% vs 1%	
COMACS Study		

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Silva 2005 United States	Single-blind RCT Placebo-controlled Crossover Multicenter	Eligible participants were children 6–12 years of age who met DSM-IV (C-DISC-4 1997) criteria for a primary diagnosis of ADHD and whose parents provided written consent for their participation in the study. Assent to participate was also obtained from all children. Inclusion criteria required that children were treated and stabilized on a total daily dose of 20–40 mg MPH for at least 2 weeks prior to enrollment. Female participants were required to be premenarchal, sexually abstinent, or using an approved method of contraception; those of childbearing potential were required to have a negative urine pregnancy test prior to enrollment. Children were ineligible to participate if they were functioning at an IQ level of 80 or below, based on the investigator's clinical judgment; if they were diagnosed with Tourette syndrome or a tic disorder; if they had a history of a seizure disorder; or if they were deemed by the investigator to be unable to understand or comply with study instructions. Children with significant concurrent medical or psychiatric illness or substance-abuse disorder, as evidenced by abnormal laborat	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Silva 2005 United States	single doses of extended-release MPH (ER-MPH) 20 and 40 mg, modified-release MPH (OROS-MPH) 18 and 36 mg, and placebo Mean Dose: NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Silva 2005 United States	NR	NR	Primary Outcome Measure: SKAMP-Attention subscale score Other Measures: SKAMP-Deportment subscale, SKAMP-Combined (Attention and Deportment) scores, and written math tests	Mean age: 9.4 yrs (SD 1.9) 63% male 63% caucasian 14.8% African American 0% Asian 22.2% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Silva 2005 United States	ADHD subtype Inattentive: 27.8% Hyperactive/impulsive: 1.9% Combined inattentive/hyperactive: 70.4%	NR/NR/54	1 withdrew

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Silva 2005 United States	Mean (SD) Postdose Scores (ER-MPH 20mg/ER-MPH 40mg/OROS-MPH 18mg/OROS-MPH 36mg/placebo) SKAMP-Attention (hours postdose) 0.5-hr: 1.70 (0.73)/1.78 (0.94)/1.97 (0.97)/1.79 (0.93)/1.86 (1.03) 1.0-hr: 1.37 (1.04)/1.37 (1.03)/1.70 (1.07)/1.76 (1.13)/2.26 (1.17) 2.0-hr: 1.08 (0.78)/0.89 (0.81)/1.31 (0.97)/1.63 (1.10)/1.79 (1.17) 3.0-hr: 1.30 (0.85)/1.01 (0.80)/1.50 (1.01)/1.65 (1.16)/2.08 (1.03) 4.0-hr: 1.31 (0.81)/1.28 (0.88)/1.57 (1.02)/1.49 (0.86)/1.95 (1.00) 6.0-hr: 1.47 (0.85)/1.21 (0.98)/1.55 (0.94)/1.60 (0.99)/2.09 (0.93) 8.0-hr: 1.75 (0.84)/1.41 (1.01)/1.64 (1.04)/1.62 (0.97)/2.18 (1.07) 10.0-hr: 1.84 (0.93)/1.74 (1.04)/1.56 (0.91)/1.81 (1.14)/2.20 (1.10) 12.0-hr: 2.13 (0.98)/1.89 (0.83)/1/73 (1.09)/1.53 (1.06)/2.22 (0.98) SKAMP-Deportment (hours postdose) 0.5-hr: 1.37 (1.29)/1.19 (1.16)/1.48 (1.21)/1.46 (1.38)/1.74 (1.49) 1.0-hr: 1.12 (1.17)/0.79 (1.08)/1.39 (1.31)/1.33 (1.42)/2.10 (1.52) 2.0-hr: 0.91 (0.95)/0.48 (0.65)/1.07 (1.12)/1.19 (1.30)/2.06 (1.46) 3.0-hr: 0.96 (0.93)/0.58 (0.74)/1.27 (1.15)/1.09 (1.10)/2.15 (1.52) 4.0-hr: 1.12 (1.05)/0.63 (0.77)/1.36 (1.24)/1.12 (1.13)/2.19 (1.41)	During each lab classroom day, vital signs and AE's were assessed. All AE's were recorded and described in terms of start and stop dates, severity of event, relationship to study drug, and any action taken for the event.

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Silva 2005 United States	Small number of AE's (18) were reported. Total AE's (ER-MPH 20mg/ER-MPH 40 mg/OROS-MPH 18 mg/OROS-MPH 36 mg/placebo: 3.7%/5.6%/9.4%/11.3%/3.8% Headache: 3.7%/1.9%/1.9%/5.7%/1.9%

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Silva 2005 United States	1 post-randomization exclusion 53/54 completed study receiving all 5 treatment conditions according to protocol	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Other comparisons to methylphenidate			
Conners, 1980	RCT DB, parallel. Setting:	Children aged 6-11.75 years, IQ >80 on WISC, physician diagnosed hyperkinesis due to minimal brain dysfunction, visual and auditory acuity was sufficient for normal learning process, family was stable, no obsessive, compulsive, or phobic behavior, child had normal laboratory values, no current medical illness or medical history that contraindicated prescribed drug therapy, no need for antiseizure medication, no concurrent therapy for a chronic illness, current ratings by parents and teachers indicating moderate to severe symptoms of restlessness, inattentiveness, impulsivity, emotional lability, and distractibility, and family physician or pediatrician consented to participate.	NR
Stephens 1984 United States Poor quality	CCT Crossover Patients recruited from (1) Psychology Clinic at Florida State University and (2) Hope Haven Children's Hospital in Jacksonville, Florida	DSM-III diagnosis of attention-deficit disorder with hyperactivity	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Other comparisons to methylphenidate	
Conners, 1980	Pemoline in 18.75mg tablets was increased weekly, by 37.5mg/day, from an initial dose of 37.5mg/day to a maximum dose of 112.5mg/day. MPH in 5mg tablets was increased weekly, by 5mg/day, from an initial dose of 10mg/day to a maximum dose of 60mg/day. Placebo. Patients were stabilized on their dose between weeks 4 and 8. The trial was 10 weeks long.
Stephens 1984 United States Poor quality	Medication was prescribed by each child's physician (method nr) Pemoline 1.9 mg/kg (mean=8.7 mg) Methylphenidate 0.3 mg/kg (mean=55.5 mg) Placebo Flexible dosing Eight 2-day treatment periods over three weeks

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Other comparisons to methylphenidate				
Conners, 1980	None/8 day washout for hyperkinesis medications and 6 months for phenothiazines	None	Parent and Teacher Conner's questionnaires, Abbreviated Parent and Teacher Conner's questionnaires, Global assessment by physician (administered at baseline, weeks 2, 4, 6, 8, and 10) and parents and teachers (administered at baseline, weeks 4 and 8), psychiatric tests which include the continuous performance test (CPT), Rutter-Graham Standardized Evaluation	Age: 7.9 years (range 6-11 years) Male: 57 (95%) White: 59 (98%) African-American: 1 (2%)
Stephens 1984 United States Poor quality	NR/NR	NR	Paired-associate learning task: Child required to give particular response (numbers 1-11) to each of a list of items (pictures of animals presented on 3 x 5 cards) Spelling task: nonsense words Testing sessions administered 2 hours after pemoline and 1 hour after methylphenidate	Mean age=8.8 86.1% male Race NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Other comparisons to methylphenidate			
Conners, 1980	NR	88/NR/60	NR/NR/60
Stephens 1984 United States Poor quality	ACRS mean score=17.9	NR/NR/31	NR/NR/NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Other comparisons to methylphenidate		
Conners, 1980	**Pemoline vs MPH vs Placebo** CPT-- For Week 0 Total trials: N=15 vs N=15 vs N=16 For Week 0 all others: N=16 vs N=16 vs N=16; For Week 8 all categories: N=18 vs N=19 vs N=17 *Total Trials:* 3.75 (327.47-323.72) vs 8.72 (331.40-322.68) vs -0.44 (324.50-324.94) *Total signals:* 0.12 (50.12-50.00) vs 0.12 (50.12-50.00) vs 0 (50.00-50.00) *Total responses,:* -9.1 (52.12-61.22) vs -7.04 (62.38-69.42) vs 7.82 (68.88-61.06) *Correct responses:* -6.44 (27.62-34.06) vs -10.62 (28.75-39.37) vs -2.09 (30.44-32.53) *Errors of omission:* 4.36 (20.75-16.39) vs 9.36 (21.31-11.95) vs 0.97 (19.56-18.59) *Errors of commission:* 1.00 (22.44-21.44) vs 4.84 (27.31-22.47) vs 9.47 (34.00-24.53) Parent Questionnaire Factors-- For Week 0: N=19 vs N=20 vs N=21; For Week 8: N=18 vs N=20 vs N=20 *Conduct problem:* 0.37 (1.14-0.77) vs 0.52 (1.16-0.64) vs 0.17 (1.00-1.17) *Anxiety:* 0.23 (0.64-0.41) vs 0.40 (0.89-0.49) vs 0.09 (0.70-0.61) *Impulsivity:* 0.54 (1.21-0.70) vs 0.84 (1.53-0.69) vs 0.14 (1.45-1.31) *Immaturity:* 0.32 (0.67-0.35) vs 0.30 (0.73-0.43) vs 0.15 (0.79-0.64) *Psychosomatic:* 0.20 (0.37-0.17) vs 0.18 (0.46-0.28) vs 0.15 (0.40-0.25) *Obsessional:* -0.18 (0.39-0.57) vs 0.20 (0.77-0.57) vs 0.07 (0.60-0.53) *Antisocial:* 0.16 (0.22-0.06) vs 0.16 (0.24-0.08) vs 0.09 (0.20-0.11) *Hyperactivity:* 0.39 (0.80-0.41) vs 0.53 (0.99-0.46) vs 0.23 (0.98-0.75) Teacher Questionnaire Factors-- For Week 0: N=19 vs N=20 vs N=21; For Week 8: N=16 vs N *Conduct problem:* 0.58 (1.11-0.53) vs 0.61 (1.29-0.68) vs 0.11 (0.82-0.71) *Inattentive-passive:* 0.80 (1.87-1.07) vs 0.66 (1.86-1.20) vs 0.40 (1.65-1.25) *Anxiety:* 0.09 (0.65-0.56) vs 0.25 (0.96-0.71) vs 0.23 (0.81-0.58) *Hyperactivity:* 0.86 (1.90-1.04) vs 0.96 (2.24-1.28) vs 0.45 (1.90-1.45) *Sociability:* 0.121 (0.53-0.41) vs 0.17 (0.88-0.71) vs -0.14 (0.76-0.90)	An ongoing record was obtained from twice-weekly phone calls to parents and physician completed a 49-item checklist of side effects on the Physician's Rating Sheet (done at weeks 4 and 8). Parents also rated their child on a 50-item checklist.
Stephens 1984 United States Poor quality	Pemoline vs methylphenidate (p=NS for all comparisons) Mean number of total errors: Paired associates learning Learning: 37.80 vs 38.64 Retention: 20.67 vs 20.58 Spelling Learning: 27.33 vs 26.19 Retention: 14.39 vs 16.42	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Other comparisons to methylphenidate	
Conners, 1980	Insomnia and sleep problems (N=29, 48%), anorexia and appetite problems (N=24, 40%), increased crying (N=20, 33%), stomachache (N=19, 32%), headache (N=13, 22%), and increased irritability (N=6, 10%). The following were reported by 4 (7%) subjects each: increased nervousness, nausea, dizziness, and rash. Moodiness was reported by 3 (5%) subjects. The following were reported by 2 (3%) subjects each: temper tantrums, thirsty, itching, depression, increased appetite, glassy eyed, nose bleed, and enuresis. The following were reported by 1 (2%) subject each: argumentative, sensitive to light, night terrors, stares glassily, fine tremors, dilated pupils, leg cramps, odd mannerism of mouth, bad dreams, increased sensitivity, diarrhea, palpitations, stuttering, negativism, nocturnal fears, eyes reddened, speech incoherent, eating erratic, grouchy, pains in ribs, and sluggishness.
Stephens 1984 United States Poor quality	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Other comparisons to methylphenidate		
Conners, 1980	NR	
Stephens 1984 United States Poor quality	NR NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Barrickman 1995 United States Fair quality	RCT Crossover Single center: ADHD outpatient clinic	Diagnosis of ADHD (DSM-III-R) and be between 7 and 17 years old	Conduct disorder = 2 (13.3%) Oppositional defiant disorder = 2 (13.3%) Developmental learning disorders = 5 (33.3%)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Barrickman 1995 United States Fair quality	Bupropion 1.5 mg/kg per day in first week, 2.0 mg/kg per day in second week, then titrated to optimal dose (mean final=140 mg) and fixed for last 3 weeks Methyphenidate 0.4 mg/kg per day during the first week, then titrated to optimal dose during next 2 weeks and fixed for final 3 weeks (mean final=31 mg/day) Duration: 6 weeks, then 2-week washout, then crossover for 6 more weeks Dosing schedule: Bupropion=active second dose was added at 4 pm and an active thirs dose was added at noon if needed; Methylphenidate=active second dose was added at noon and a third dose was added at 4 pm if needed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Barrickman 1995 United States Fair quality	No run-in/Washout of 14 days	NR	Iowa Conners Abbreviated Parent and Teacher Questionnaire (ICQ); physician-rated Clinical Global Impression (CGI)	Mean age of 11.8 80% male 100% Caucasian

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Barrickman 1995 United States Fair quality	Treatment-naïve=5 (33.3%) WISC-R Full Scale IQ score=106 WISC-R Verbal score=104 WISC-R Performance score=108	NR/NR/18	3 (16.7%) withdrawn/0 lost to fu/15 analyzed

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Barrickman 1995 United States Fair quality	Bupropion vs methylphenidate ICQ change scores (between-group differences not significant unless otherwise noted) Total Teachers: -12.7 vs -14.5; Parents: -11.2 vs -15 Attention Teachers: -6.3 vs -7.6; Parents: -5.9 vs -8.5 ("significant", but no p-value provided) Conduct Teachers: -6.7 vs -7.5; Parents: -5.5 vs -6.4 CDI: -4.1 vs -3.9; R-CMAS: -9 vs -8.1 Kagen errors: -5.5 vs -7; Kagen latency: -6.3 vs -4.8 CPT omission errors: -3.1 vs -4; CPT commission errors: -5.5 vs -6.9 AVLT: -6.1 vs -8.8; CGI (week 5): -2.1 vs -2.6; p<0.05, changes from baseline to other weeks similar for both drugs	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Barrickman	Bupropion vs MPH
1995	% patients with any adverse event: 9 (60%) vs 5 (33.3%); p=NS
United States	Drowsiness: 4 (26.7%) vs 1 (6.7%)
	Fatigue: 3 (20%) vs nr
Fair quality	Nausea: 3 (20%) vs 1 (6.7%)
	Anorexia: 2 (13.3%) vs nr
	Dizziness: 2 (13.3%) vs nr
	Spaciness: 2 (13.3%) vs nr
	Anxiety: 1 (6.7%) vs 1 (6.7%)
	Headache: 1 (6.7%) vs 1 (6.7%)
	Tremor: 1 (6.7%) vs nr
	Anger/crying: nr vs 1 (6.7%)
	Insomnia: nr vs 1 (6.7%)
	Irritability: nr vs 1 (6.7%)
	Low mood: nr vs 1 (6.7%)
	Stomachache: nr vs 1 (6.7%)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Barrickman 1995 United States Fair quality	Total withdrawals: 3 (16.7%) (group assignments nr) Withdrawals due to adverse events: none reported	Significant treatment order effects were reported

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Multiple Comparisons			
James 2001 United States Poor	RCT Crossover Double-blind Setting: Research school 5 days per week	DSM-IV criteria for combined-type ADHD; ADHD symptoms present in at least two settings	Oppositional defiant disorder=10 (28.6%) Anxiety disorder=12 (34.3%) Enuresis=3 (8.6%) Dysthymic disorder=2 (5.7%) Learning disorder=6 (17.1%)
Pelham 1990 Poor	RCT Crossover 1988 Western Psychiatric Institute and Clinic Attention Deficit Disorder Program's Summer Treatment Program	Diagnosis of ADHD based on structured parental interview and parent and teacher rating scales (not specified)	Oppositional/defiant disorder = 9 (40.9%) Conduct Disorder = 4 (18.2%) Discrepancy between their Wechsler Intelligence Scale for Children-Revised IQ and their Woodcock-Johnson Achievement socres of at least one full standard deviation in either reading, arithmetic, or written language, suggesting the presence of a learning disability = 13 (59.1%)
Atomoxetine			

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Multiple Comparisons	
James 2001 United States Poor	Adderall Dextroamphetamine, immediate release Dextroamphetamine spansules Placebo 2 weeks each Dosages were based on age, weight, prior medication experience, and symptom severity. Overall mean low dose was 7.8 mg and mean high dose was 12.8 mg. Dose order was randomized across subjects, but the same order, either increasing (n=18) or decreasing (n=17) was used for a given subject. The last 11 subjects received equal doses of both immediate-release formulations, but received increased dextroamphetamine spansules by 5 mg to more closely approximate clinical use patterns.
Pelham 1990 Poor	Methylphenidate IR 20 mg (dosed twice daily) Sustained release methylphenidate 20 mg (dosed once daily) Pemoline 56.25 mg (dosed once daily) Sustained release dextroamphetamine (dexedrine spansule) 10 mg (dosed once daily) All conditions accompanied by "behavior modification intervention" as the "primary treatment modality" 8 weeks total, data collected for 3 to 6 days for each condition Dosage time NR

Atomoxetine

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Multiple Comparisons				
James 2001 United States Poor	Run-in NR/3-week washout	NR	Hyperactive/Impulsive factor of the Conners Teacher Rating Scale: teacher Hyperactivity factor of the Children's Psychiatric Rating Scale: recreation therapist scored weekly Academic measures: 5-minute timed math task Conners Parent Behavior Rating Scale for the hours 4 pm to 7 pm Actometer to assess motor activity	Mean age=9.1 60% male 18 (51.4%) White 9 (25.7%) African Americans 7 (20%) Latinos 1 (2.8%) Asian Americans
Pelham 1990 Poor	NR/NR	NR	Daily Frequencies=frequencies with which numerous appropriate and inappropriate behaviors occurred daily Classroom measures=rates of on-task behavior and rule-following behavior; 2-minute, timed arithmetic drill, 10-minute, timed reading task (number attempted and percentage correct) Rating scales: Teacher ratings on ACTRS; counselor ratings on Revised Behavior Problems Checklist (35 items rated on a 7-point scale with lower ratings equalling positive evaluations) Daily Report Card=Percentage of days that the child reached daily report criterion Continuous Performance Task="H" followed by letter "T"	Mean age=10.39 100% male Race NR
Atomoxetine				

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Multiple Comparisons			
James 2001 United States Poor	15 (42.8%) naïve to stimulant treatment WISC-III Verbal standard score=102.5 Performance standard score=96.6 Full scale standard score=99.8 CBCL Attention Problems T score=72.5 TRF Attention Problems T score=72.3	NR/38 enrolled/35 randomized	0/0/35
Pelham 1990 Poor	WISC-R IQ=105.68 ACRS - Parent/Teacher: 15.50/19.32 IOWS CTRS Inattention/Overactivity=9.59 Aggression=5.86 DSM-II-R Structured Interview for Parents Attention deficit disorder items=11.36 Oppositional/defiant disorder items=5.36 Conduct disorder items=1.68 Woodcock-Johnson Achievement Test Reading=96.45 Mathematics=99.82 Language=99.00	NR/NR/22	NR/NR/NR

Atomoxetine

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Multiple Comparisons		
James 2001 United States Poor	Adderall vs dextroamphetamine spansules vs immediate release dextroamphetamine vs placebo; differences are insignificant unless otherwise noted CTRS Hyperactivity T score obtained from 9 AM to 12:30 PM: 50.6 vs 53.7 vs 50.5 vs 63.1; DEX IR > DEX span, p<0.025 CPRS Hyperactivity factor score obtained between 1 PM and 3 PM: 2.8 vs 2.3 vs 2.5 vs 3.8; DEX span > ADL, p=0.04 CPS Hyperactivity T score obtained between 4 PM and 7 PM (only available for n=15): 58.6 vs 60.0 vs 60.5 vs 68.0; Dex span > placebo (p=0.007), ADL > placebo (p=0.03), DEX IR = placebo Total attempted math problems: 171.6 vs 187.0 vs 177.4; DEX IR > placebo (p=0.01), DEX span > placebo (p=0.003), ADL = placebo Total correct math problems: 164.6 vs 177.6 vs 167.6 vs 140.2; DEX IR > placebo (p=0.01), DEX span > placebo (p=0.003), ADL=placebo Sleep (hr): 7.6 vs 7.2 vs 7.4 vs 7.8; DEX span and DEX IR decreased sleep > placebo (p<0.001 and p=0.02), ADL=placebo	Stimulant Side Effect Rating Scale: rated by nurse coordinator Barkley Side Effect Rating Scale: rated by parents
Pelham 1990 Poor	Placebo vs Methylphenidate vs sustained release methylphenidate vs pemoline vs sustained release dextroamphetamine, ALL results significant compared to PLACEBO unless otherwise noted (p=NS): Daily frequency measures: % following activity rules: 75.2 vs 80.9 vs 78.1 vs 79.0 vs 81.0 Noncompliance: 5.5 vs 2.3 vs 2.3 vs 2.0 vs 1.7 Positive peer interactions: 82.8 vs 92.6 (p=NS) vs 104.5 vs 111.1 vs 100.0 Conduct problems: 0.73 vs 0.25 (p=NS) vs 0.18 vs 0.18 vs 0.21 Negative verbalizations: 5.4 vs 1.6 vs 2.0 (p=NS) vs 1.6 vs 1.4 Classroom measures: % following rules: 85 vs 92 (p=NS) vs 94 vs 95 vs 95 Timed reading # attempted: 14.3 vs 18 vs 16.4 vs 15.7 vs 17.5 % correct: 69 vs 73 vs 73 vs 75 vs 74 Seatwork % completed: 70 vs 78 vs 77 vs 79 (p=NS) vs 76 % correct: 84 vs 84 vs 87 (p=NS) vs 87 vs 86 Teacher rating (ACTRS): 3.8 vs 2.3 vs 2.3 vs 1.5 vs 1.7 Counselor rating (ACTRS): 6.3 vs 4.8 vs 5.0 vs 5.1 vs 4.5 Positive daily report (% days rec'd): 51 vs 63 (p=NS) vs 64 vs 71 vs 67	NR

Atomoxetine

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Multiple Comparisons	
James 2001 United States Poor	SERS N#: 3.3 vs 2.9 vs 2.6 vs 2.0 SERS-N sev: 2.7 vs 3.1 vs 2.7 vs 1.8 SERS-P#: 6.3 vs 6.7 vs 6.4 vs 5.9 SERS-P sev: 3.2 3.7 vs 3.2 vs 2.8 Weight (kg): 32.6 vs 32.5 vs 32.7 vs 33.3 Mean magnitude of adverse effects rated by parents (n=20); staff nurse (n=29) for adderall, immediate-release dextroamphetamine, dextroamphetamine spansules and placebo, uncorrected p-values from ANOVA Trouble sleeping: 3.5 vs 3.0 vs 3.3 vs 2.5, p=0.55; nurses didn't rate Nightmares: 0.6 vs 0.6 vs 0.3 vs 0.3, p=0.24 Stomaches: 1.0 vs 0.9 vs 1.1 vs 1.0, p=0.97; 0.5 vs 0.5 vs 0.8 vs 0.4, p=0.59 Headaches: 0.9 vs 0.8 vs 0.7 vs 1.0, p=0.89; 0.1 vs 0.2 vs 0.2 vs 0.1; p=0.41 Tics: 0.8 vs 1.2 vs 1.4 vs 0.9; p=0.16; 0.4 vs 0.3 vs 0.3 vs 0.2, p=0.34
Pelham 1990 Poor	Placebo vs Methylphenidate vs sustained release methylphenidate vs pemoline vs sustained release dextroamphetamine, measures of significance NR: <u>Teacher ratings</u> Withdrawn: 0 vs 10.0 vs 0 vs 0 vs 13.6 Dull, not alert: 4.5 vs 14.3 vs 4.3 vs 0 vs 9.0 Stomachaches, nausea: 13.6 vs 14.3 vs 9.1 vs 10.0 vs 22.7 Headaches: 9.1 vs 0 vs 0 vs 0 vs 22.7 Loss of appetite: 45.0 vs 61.9 vs 76.2 vs 75 vs 77.3 Eye/Muscel twitches: 4.5 vs 4.8 vs 9.1 vs 4.89 vs 4.5 Repetitive tongue movements: 9.1 vs 4.8 vs 0 vs 5.0 vs 4.5 Picking: 0 vs 0 vs 0 vs 0 vs 4.5 <u>Parent ratings</u> Difficulty falling asleep: 5.3 vs 5.9 vs 18.8 vs 42.1 vs 20.0 Awake during the night: 5.3 vs 12.5 vs 13.3 vs 11.1 vs 14.3

Atomoxetine

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Multiple Comparisons		
James 2001 United States Poor	0 withdrawals; 0 withdrawals due to adverse events	
Pelham 1990 Poor	NR NR	

Atomoxetine

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Kratochvil 2002 United States/Canada Fair	Open-label Parallel Multicenter Outpatient	Boys aged 7 to 15 years and girls aged 7 to 9 years who met DSM-IV diagnostic criteria for ADHD. Diagnosis was confirmed by clinical interview and by structured interview with the Schedule for Affective Disorders and Schizophrenia for School-Age Children ADHD module. All patients had a severity score of at least 1.5 standard deviations above age and gender norms on the ADHD-IV Rating Scale-Parent Version: Investigator Administered (ADHD RS)	Oppositional/defiant disorder = 52.6% Major depressive disorder = 6.6% Elimination disorder = 16.7%

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Kratochvil 2002 United States/Canada Fair	Atomoxetine CYP 2D6 extensive metabolizers: titrated to a maximum of 2 mg/kg per day and administered as a divided dose in the morning and late afternoon (mean=1.40 mg/kg per day) CYP 2D6 poor metabolizers: Initiated at 0.2 mg/kg per day and titrated to 1.0 mg/kg per day (mean=0.48 mg/kg per day) Methylphenidate: Beginning at 5 mg from one to three times daily with an ascending dose titration based on the investigators assessment of clinical response/tolerability; maximum dose of 60 mg (mean dose=0.85 mg/kg per day) 10 weeks

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Kratochvil 2002 United States/Canada Fair	NR/NR	NR	Primary measure: Investigator-rated ADHD RS Secondary measures: Parent-rated version of the ADHD RS; Conners Parent Rating Scale-Revised: Short Form (CPRS-R); Clinical Global Impression-ADHD-Severity scale	Mean age=10.4 92.5% male 76.7% white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Kratochvil 2002 United States/Canada Fair	ADHD subtype Combined: 75.9% Hyperactive-impulsive: 1.3% Inattentive: 22.8% ADHD RS-Parent scored (mean): 76.7	319/NR/228	85 (37.3%) withdrawn/5 (2.2%) lost to fu/218 analyzed (atomoxetine n=178; methylphenidate n=40)

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Kratochvil	Atomoxetine vs methylphenidate (mean changes) (p=NS for all)	Administration of open-ended questions and collection of ECG and laboratory data
2002	ADHD RS Total score: -19.44 vs -17.78	
United States/Canada	ADHD RS Hyperactivity/Impulsivity: -9.50 vs -8.48	
	ADHD RS Inattention subscale: -9.94 vs -9.30	
Fair	CGI-ADHD-Severity score: -1.67 vs -1.70	
	CPRS-R ADHD Index: -11.36 vs -11.97	
	CPRS-R Cognitive: -6.17 vs -5.69	
	CPRS-R Hyperactive: -5.56 vs -4.78	
	ADHD RS-Parent Total T score: -18.83 vs -18.38	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Kratochvil 2002 United States/Canada Fair	Atomoxetine vs methylphenidate; p=NS unless otherwise noted Headache: 57 (31%) vs 13 (32.5%) Abdominal pain: 43 (23.4%) vs 7 (17.5%) Anorexia: 35 (19%) vs 6 (15%) Rhinitis: 33 (17.9%) vs 8 (20%) Nervousness: 29 (15.8%) vs 4 (10%) Vomiting: 22 (12%) vs 0, p=0.017 Fever: 20 (10.9%) vs 4 (10%) Somnolence: 20 (10.9%) vs 0, p=0.029 Nausea: 19 (10.3%) vs 2 (5%) Insomnia: 17 (9.2%) vs 7 (17.5%) Asthenia: 14 (7.6%) vs 1 (2.5%) Diarrhea: 13 (7.1%) vs 1 (2.5%) Emotional lability: 11 (6%) vs 2 (5%) Pharyngitis: 11 (6%) vs 3 (7.5%) Tachycardia: 11 (6%) vs 2 (5%) Accidental Injury: 10 (5.4%) vs 5 (12.5%) Cough increased: 10 (5.4%) vs 2 (5%) Dyspepsia: 10 (5.4%) vs 2 (5.0%) Pain: 10 (5.4%) vs 1 (2.5%) Flu syndrome: 9 (4.9%) vs 4 (10%) Infection: 8 (4.3%) vs 3 (7.5%) Rash: 7 (3.8%) vs 3 (7.5%) Depression: 5 (2.7%) vs 2 (5%) Weight loss: 5 (2.7%) vs 2 (5%) Hyperkinesia: 3 (1.6%) vs 2 (5%) Palpitation: 3 (1.6%) vs 2 (5%) Thinking abnormal: 0 vs 2 (5%); p=0.031

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Kratochvil 2002 United States/Canada Fair	Total withdrawals: 66 (35.9%) vs 19 (43.2%); p=NS Withdrawals due to adverse events: 10 (5.4%) vs 5 (11.4%); p=NS	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Kemner 2005 United States Poor	Open-label Parallel Multicenter Outpatient	Children 6 to 12 years of age; meet criteria for a primary diagnosis of ADHD (any subtype) according to the DSM-IV-TR; investigator-rated ADHD-RS score of at least 24 and a Clinical Global Impression-Severity of Illness scale (CGI-S) score of at least 4 ("moderately ill" or worse)	NR

FOCUS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Kemner 2005 United States Poor FOCUS	Mean dosages for weeks 1/2/3: Atomoxetine: 32.1 mg/36.8 mg/36.7 mg OROS MPH: 26.8 mg/32.7 mg/32.7 mg (Investigators were allowed to select starting doses and adjust dosages as deemed necessary) Duration: 3 weeks

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Kemner 2005 United States Poor FOCUS	NR/Wash-out: 3 days or 5 half-lives	NR	Primary measure: Mean change from baseline in investigator-rated ADHD RS Secondary measures: ADHD-RS and CGI-I scores assessed at weeks 1 and 2; proportion of treatment responders at each evaluation point, defined as those patients who achieved a 25% or greater reduction from baseline ADHD-RS score, as well as those receiving an investigator-rated CGI-I score of 2 or less ("much improved" or "very much improved"); treatment response further evaluated on basis of ADHD-RS baseline score reductions of 30% or greater, 50% or greater, and 70% or greater; parent ratings of a nonvalidated, newly developed diary, the Parental Satisfaction Questionnaire (PSQ) (9 statements regarding the patient's behavior, each rated by parents on a 5-point scale ranging from 1=strongly agree to 5=strongly disagree; maximum score=45)	Mean age=8.9 years 74% male 76.74 white

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Kemner 2005 United States Poor FOCUS	ADHD subtype Combined: 72% Hyperactive-impulsive: 15% Inattentive: 13% ADHD RS-Investigator-scored (mean): 39.3	NR/NR/1323	NR/NR/NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Kemner	OROS MPH vs atmoxetine:	Spontaneous patient reports and/or parents;
2005	ADHD RS Total score (mean change in points): -20.24 vs -16; mean difference=4.24 (p<0.001)	identification by investigators during
United States	ADHD-RS responder rates (% pts with 25% or greater reduction in ADHD-RS): 80.2% vs	scheduled study visits
Poor	68.7%; p<0.001	
	CGI-I responder rates (% pts with scores of 2 or lower): 68.6% vs 52.8%; p<0.001	
FOCUS	PSQ mean reductions (points): -9.1 vs -8.7; p<0.001	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Kemner 2005 United States Poor FOCUS	OROS MPH vs atomoxetine (%) - NS unless otherwise noted: Overall AE incidence: 26.3% vs 28.3% Serious AEs (resulting in prolonged inpatient hospitalization, significant disability or incapacity, onset of life-threatening conditions: 0.8% vs 0.2% Abdominal pain: 0.4 vs 1.1 Abdominal pain, upper: 3.5 vs 4.2 Abnormal behavior: 1.4 vs 1.5 Aggression: 1.2 vs 0.6 Crying: 1.5 vs 0.4 Decreased appetite*: 5.8 vs 3.0 Dizziness: 0.8 vs 1.5 Emotional disturbance: 0.6 vs 1.1 Fatigue*: 0.4 vs 3.0 Headache: 3.9 vs 4.2 Initial insomnia: 1.1 vs 0.2 Insomnia: 6.2 vs 2.3 Irritability: 0.8 vs 1.5 Mood alteration: 1.2 vs 1.3 Nausea*: 1.1 vs 4.9 Somnolence*: 0.9 vs 4.2 Vomiting: 1.3 vs 2.1 *=difference noted in text, but p-value NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Kemner 2005 United States Poor FOCUS	Withdrawals due to adverse events: 4.8% vs 5.5%, p-value NR Overall withdrawals NR	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Starr 2005 United States Subanalysis of FOCUS	Open-label Parallel Multicenter Outpatient	See Kemner 2005; African American group only	See Kemner 2005

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Starr 2005 United States Subanalysis of FOCUS	Mean dosages: 32.5 mg vs 1.1 mg/kg/day

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Starr 2005 United States Subanalysis of FOCUS	See Kemner 2005	See Kemner 2005	See Kemner 2005	Mean age=8.8 years 82% male 100% African American

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Starr 2005 United States Subanalysis of FOCUS	ADHD subtype Hyperactive-impulsive: 14.1% Inattentive: 9.1% Combined: 14.7% Family history of ADHD: 47% Prior treatment for ADHD: 52% Duration of ADHD: 27 months Baseline ADHD-RS: 40.6 Baseline CGI-SI: 4.9	NR/NR/183 (OROS MPH n=125; atomoxetine n=58)	NR/NR/NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Starr 2005 United States Subanalysis of FOCUS	OROS MPH vs atmoxetine: ADHD RS Total score (mean change in points): Week 1: -9.8 vs -7.5, NS Week 2: -14.5 vs -11.4; NS Week 3: -20.4 vs -15.9; p<0.03 ADHD-RS responder rates ≥ 30% reductions (% pts): 77.4% vs 61.1%; p<0.03 ≥ 50% reductions (% pts): 58.3% vs 35.2%: p<0.006 CGI-I responder rates (% pts with scores ≤2): 68.4% vs 49.1%; p<0.01 PSQ total scores: 19.8 vs 23.4; p<0.009 % parents stating that their child was doing "better than" or "somewhat better than" before treatment: 85.1% vs 63.8%; p-value NR	See Kemner 2005

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported
Starr 2005 United States Subanalysis of FOCUS	Treatment-related adverse events: 19.2% vs 19% Upper abdominal pain: 4.8% vs 1.7% Decreased appetite: 4% vs 1.7% Headache: 4.0% vs 1.7% Insomnia: 3.2% vs 0 Nausea: 0.8% vs 3.4% Somnolence: 0.8% vs 5.2% Sedation: 0 vs 5.2% p-values NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Starr 2005 United States	Withdrawals due to adverse events: 0.8% vs 1.7%; p-value NR Overall withdrawals NR	

Subanalysis of FOCUS

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Wigal 2005 United States Fair StART study	Double-blind Parallel Multicenter Simulated classroom setting	Male or female aged 6 to 12 years; diagnosis of DSM-IV-TR ADHD combined subtype or predominantly hyperactive/impulsive subtype; weight between 40 lb and 120 lb at enrollment; and capable of understanding and following classroom instruction and generally functioning academically at age-appropriate levels	NR
Biederman 2006 StART substudy (Wigal 2005)	See Wigal 2005	Subgroup of girls from Wigal 2005. See above for eligibility criteria	N/A

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Wigal 2005 United States Fair StART study	Atomoxetine: wk1=0.5 mg/kg/d; wk2-3=1.2 mg/kg/d Mixed amphetamine salts (MAS) XR: wk1=10 mg; wk2=20 mg; wk3=30 mg (mean dosages NR) Duration=3 weeks (wk)
Biederman 2006 StART substudy (Wigal 2005)	See Wigal 2005

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Wigal 2005 United States Fair StART study	4-day single-blind placebo lead-in period/washout of previous medications, but no details provided	NR	Primary: Change in mean SKAMP deportment subscale scores Secondary: mean SKAMP deportment subscale scores; 10-minute age-appropriate math tests (absolute number of problems attempted and the absolute number of problems completed correctly); CGI; CGI-S; CGI-I; 10-item Conners' Global Index Scale-Parent version (CGIS-P); Medication Satisfaction Survey (Med-SS); Pediatric Quality of Life Inventory (PedsQL)	Mean age=8.7 years 71.9% male 55.6% white 16.2% black 19.7% hispanic 2.0% asian or pacific islander 6.4% other
Biederman 2006 StART substudy (Wigal 2005)	See Wigal 2005	See Wigal 2005	See Wigal 2005	Mean age=8.7 years Subgroup of 100% girls 59.1% white 22.8% black 17.5% hispanic 1.8% asian/pacific islander 8.8% other

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Wigal 2005 United States Fair StART study	ADHD subtype Hyperactive/impulsive: 0.5% Combined: 99.5% CGI-S category: Borderline impairment: 2.5% Mildly impaired: 3.9% Moderately impaired: 60.1% Markedly impaired: 25.6% Severely impaired: 9.3%	NR/NR/215	25 (12.3%) withdrawn/LTFU NR/203 (94.4%) (MAS XR n=102; atomoxetine n=101)
Biederman 2006 StART substudy (Wigal 2005)	Mean weight (lb): 71.98 ADHD subtype Hyperactive/impulsive: 0% Combined: 100%	NR/NR/57	NR/NR/57

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Wigal 2005 United States Fair StART study	MAS XR vs atomoxetine SKAMP scale mean changes Deportment: -0.56 vs -0.13; p<0.0001 Attention: -0.49 vs -0.08; p<0.0001 SKAMP scale responders Deportment (≥ 25% improvement): 70% vs 38%; p≤0.0001 Attention (≥ 25% improvement): 68% vs 28%; p<0.0001 Math problems (mean number) Attempted: 62.6 vs 30.5; p<0.0001 Completed correctly: 61.6 vs 29.0; p<0.0001 CGIS-P mean decrease in unit points: -8.3 vs -6.63; p=NS CGI-I ratings of very much improved/much improved (% pts): 74.5% vs 35.6%; p<0.0001 PedsQL total score mean increase in unit points: +7.1 vs +7.9; p=NS PedsQL school functioning score increase in unit points (% increase): +34% vs +25%; p=0.0026 Parent-Rated Med-SS: MAS XR=atomoxetine (data NR)	Assessed by spontaneously reported adverse events
Biederman 2006 StART substudy (Wigal 2005)	MAS XR vs atomoxetine SKAMP scale mean changes Deportment: -0.48 vs -0.04; p<0.001 Attention: -0.45 vs -0.05; p<0.001 Math problems (mean number) Attempted: 135.27 vs 119.72; p<0.04 Completed correctly: 94.4% vs 96%; NS	See Wigal 2005

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Wigal 2005 United States Fair StART study	MAS XR vs atomoxetine (p-values NR for all; those reported below reflect Oregon EPC calculations using StatsDirect) Overall AE incidence: 85% vs 73.1%; NS Upper abdominal pain: 18.7% vs 14.8% Vomiting: 4.7% vs 13%; p=0.035 Fatigue: 1.9% vs 7.4% Nausea: 6.5% vs 9.3% Weight decrease: 5.6% vs 3.7% Anorexia: 16.8% vs 9.3% Appetite decrease: 28% vs 17.6% Dizziness: 5.6% vs 1.9% Headache: 15% vs 10.2% Somnolence: 4.7% vs 18.5%; p=0.0015 Insomnia: 28% vs 7.4%; p<0.0001	Overall withdrawals: 13.1% vs 10.2%; NS AE withdrawals: 6.5% vs 3.7%; NS	
Biederman 2006 StART substudy (Wigal 2005)	MAS XR vs atomoxetine (p-values NR) Appetite decrease: 40.7% vs 12.5% Upper abdominal pain: 29.6% vs 15.6% Insomnia: 25.9% vs 3.1% Headache: 14.8% vs 9.4% Weight decrease: 7.4% vs 0 Anorexia: 7.4% vs 6.3% Nausea: 3.7% vs 12.5% Vomiting: 3.7% vs 15.6% Somnolence: 3.7% vs 28.1% Fatigue: 0 vs 6.3% Any adverse event: 78% vs 66%	Overall withdrawals: NR AE withdrawals: 7% vs 3%	

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Prasad 2007		Patients were children and adolescents who met DSM-IV criteria for ADHD by clinical investigator assessment and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Versions (K-SADS-PL). Children were 7–15 years of age, and were not intellectually impaired in the viewpoints of the investigators. They were required to have a symptom severity score ≥ 1.5 standard deviations above the investigator-rated ADHD-Rating Scale-IV (ADHD-RS) age norm for their ADHD subtype to be eligible for enrolment. Patients were assessed for other psychiatric disorders by clinical assessment and by the K-SADS-PL (disruptive behaviours, anxiety, and affective disorders modules). Patients were excluded if they weighed < 20 kg; had a history of bipolar disorder, psychotic disorders, pervasive development disorder (autistic spectrum disorder), any seizure disorder or alcohol/drug abuse; were with significant prior/current medical conditions or at serious suicidal risk; or were taking medication that could potentially interfere with study outcomes. Females who were pregnant/breastfeeding or sexually active a contraception were also excluded.	
Sangal 2006 United States	RCT, DB Crossover 2 sleep disorder centers	Patients were 6 to 14 years old at study entry. They were diagnosed with ADHD using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria as well as severity criteria. Diagnosis was assessed by the investigator's clinical evaluation and by the administration of several modules of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version structured interview. In addition, patients had an ADHD Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHD RS) score at least 1.0 standard deviation above normative values for age and sex for either the inattentive or hyperactive/impulsive subscore, or for the combined score. All patients scored at least 80 on the Wechsler Intelligence Scale for Children -3rd edition. Important exclusion criteria included serious medical illness, a history of symptoms suggestive of a primary sleep disorder – such as obstructive sleep apnea (OSA) (e.g., habitual snoring), periodic limb movement disorder (PLMD, eg, kicking movements during sleep), or insufficient sleep syndrome (e.g., voluntary sleep restriction resulting in sleep durati shorter than expected age norms}--that could potentially result in a daytime symptom constellation similar to ADHD, and abnormal laboratory values or electrocardiogram (ECG) readings. Patients agreed not to use caffeinated beverages during the duration of the study.	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Interventions and total daily dose Duration Dosing schedule
Prasad 2007	Atomoxetine: Mean Dose: 1.5 mg/kg/day. commenced on 0.5 mg/kg/day. After a minimum of 7 days, patients who, in the judgement of the investigator, had clinically significant residual symptoms and who were tolerating atomoxetine, could have a dose increase to approximately 1.2 mg/kg/day. After a minimum of two further weeks, a dose increase to a maximum of 1.8 mg/kg/day was permitted, if required, based on the investigator's assessment of clinical response (efficacy and tolerability) SCT: Mean daily dose of single therapy shortacting MPH was 0.80 mg/kg/day, and for long-acting OROS MPH was 1.03 mg/kg/day. SCT was defined as any intervention regarded by the investigator/treating physician that would benefit the patient, and that they would use as appropriate in their standard clinical practice, including the option of no therapy. SCT could include any combination of medicines (apart from atomoxetine) and/or simple behavioural counselling approaches
Sangal 2006 United States	Atomoxetine Mean final dose: 58.27 mg/day (range = 15-100), or 1.56mglkg per day Methylphenidate: Mean final dose was 42.29 mg/day (range = 15-60), or 1.12 mglkg per day

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Prasad 2007			Primary Outcome Measure: Parent-Rated Child Health and Illness Profile-Child Edition (CHIP-CE) total (global) t-score Other Measures: the five CHIP-CE domains; parent-rated Family Burden of Illness Module (FBIM); investigator-rated ADHD-Rating Scale; investigator-rated Clinical Global Impression (CGI)-Severity/Improvement scales; and childrated Harter Self-Perception Profile (HSPP)	Mean age: 10.9 yrs (SD 2.2) (Range: 6.9-15.9 yrs) 88.6% male 99% caucasian
Sangal 2006 United States	10-20 day study-drug washout	NR	Primary Outcome Measure: change from baseline to endpoint in sleep-onset latency, as measured by actigraphy Other Measures: ADHD RS (Visit 1 and at the end of each study period), the Clinical Global Impression-Severity scale (Visits 1 and 3-12), the Conners' Parent Rating Scale-Revised: Short Form (CPRS-R:S) (Visit 1 and at the end of each study period), and the Daily Parent Ratings of Evening and Morning Behavior (DPREMB) (Visits 1-3,6,7, 11, and 12)	Mean age: 10.1 yrs (SD 2.0) 75.3% male 72.9% caucasian

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Prasad 2007			
Sangal 2006 United States	ADHD Sybtype: Hyperactive/Impulsive: 2.4% Inattentive: 29.8% Combined: 67.9% Present Comorbid Conditions: ODD: 48.2% Conduct Disorder: 3.5% Anxiety Agoraphobia: 1.2% Prior stimulant exposure: 56.5%	107/85/85	6 withdrew after 1st acute treatment phase; 4 withdrew after 2nd acute treatment phase 50 analyzed (25 excluded from analysis) n=79 for safety

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Results	Method of adverse effects assessment
Prasad 2007		
Sangal 2006 United States	Actigraphic Sleep Measures Change from Baseline (SD) Atomoxetine vs. Methylphenidate; [95% CI] Sleep-onset latency, min: 12.06 (27.07) vs. 39.24 (40.77); p<0.001 [-12.82, -6.49] Total nap time, min: 4.49 (10.41) vs. 3.04 (7.92); p=0.475 [-1.68, 3.55] Total sleep interval, min: -15.00 (45.10) vs. -35.89 (56.10); p=0.004 [6.81, 34.15] Assumed sleep time, min: -15.26 (44.25) vs. 29.61 (53.00); p=0.016 [2.73, 25.73] Interrupted sleep time, min: 0.26 (15.04) vs. -6.28 (17.48); p=0.025 [0.80, 11.69] Sleep interruptions, no.: -1.31 (6.83) vs. -4.36 (6.33); p=0.011 [0.70, 5.19]	NR

Evidence Table 3. Head-to-head trials in children with ADHD

Author, year	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Prasad 2007			
Sangal 2006 United States	TEAs ocurring in at least 10% of the 79 patients in either treatment group (Atomoxetine vs. Methylphenidate) Decreased appetite: 11.4% vs. 24.1% (p=0.30) Headache: 19.0% vs. 15.2% (p=0.698) Insomnia: 6.3% vs. 26.6% (p<0.001) Appetite decreased: 11.4% vs. 15.2% (p=0.357) Irritability: 11.4% vs. 15.2% (p=0.263) Pharyngtis: 15.2% vs. 8.9% (p=0.173) Cough: 12.7% vs. 8.9% (p=0.625) Somnolence: 15.2% vs. 3.8% (p=0.057) Abdominal pain, upper: 11.4% vs. 5.1% (p=0.248) Fatigue: 11.4% vs. 3.8% (p=0.121)	No withdrawals due to adverse events; total withdrawals depends on which phase of the study	

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Arnold 1978 Huestis 1975	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Barkley 2000	NR	NR	Crossover	Yes	Yes	Yes	Yes	Reported that 20 - 31% completed each randomized order of drug administration
Barrickman 1995	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	Yes NR NR NR
Bergman 1991	Inadequate (counterbalanced order)	NR	n/a - crossover	No	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Arnold 1978 Huestis 1975	NR	Yes	No	Fair	NR/NR/29	NR	2-week placebo washout
Barkley 2000	NR	No	1 excluded due to low IQ	Poor	NR/NR/46	History of (1) motor/vocal tics or Tourette's Syndrome; (2) cardiac surgery, high blood-pressure (sustained blood-pressure levels above the 95th percentile for age and sex) at baseline, or cerebral vascular accident, given the known cardiac presser effects of stimulant medication; (3) adverse reactions to stimulant medications; (4) hyperthyroidism; (5) pregnancy/lactation.	NR/NR
Barrickman 1995	NR/NR	No; 3 (16.7%) excluded from analysis that were dropped due to failure to cooperate	No	Fair	NR/NR/18	IQ < 70 (mental retardation) and any other major Axis I, II, or III diagnoses; seizure disorder; eating disorder.	No run-in; 14-day washout
Bergman 1991	NR	Unclear	Unclear	Poor	NR/NR/42	NR	NR/NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Arnold 1978 Huestis 1975	65.5% were psychopharmacologically "virgin"	Yes	Grant from Ohio Department of Mental Health and Mental Retardation; matched dosage forms were furnished by Ciba-Geigy Pharmaceutical Corp.	No; high proportion of class naïve patients
Barkley 2000	NR	Yes	Shire	Yes
Barrickman 1995	No	Yes	NR	Yes
Bergman 1991	NR	Yes	NIMH Grants (MH 38838-05 and MH 30906-09)	Unclear

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Borcherding 1990	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Casellanos 1997	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Conners 1980	NR	NR	No	Yes	Yes	Yes	Yes	NR NR NR NR
Connor 2000	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR
Cox 2004	Yes, random numbers table	NR; Use of a random number table without a 3rd party may indicate lack of allocation concealment	n/a - crossover	Yes	Unclear (abstract states study was single-blind, no other details)	Unclear (abstract states study was single-blind, no other details)	Unclear (abstract states study was single-blind, no other details)	Yes NR NR NR
Efron 1997	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Borcherding 1990	NR	No	Unclear	Poor	NR/NR/46	Medical or neurological disease, including chronic motor tics or Tourette's syndrome, or other primary Axis I psychiatric disorder were exclusionary.	No/Yes
Casellanos 1997	NR	No	Unclear	Poor	NR NR Enrolled: Group 1=22, Group 2=6, Group 3=4	WISC-R Full Scale IQ score less than 75; evidence of medical or neurological diseases; any other Axis I psychiatric disorder, except obsessive-compulsive disorder, conduct or oppositional disorder, overanxious disorder, and specific developmental disorders.	≥ 4 weeks washout
Conners 1980	Unclear	Unclear	No	Fair	88/60/60	NR	NR
Connor 2000	No	Yes	No	Fair	NR/NR/24	NR	NR
Cox 2004	No/No	No	No	Fair	NR/NR/7	History of tics or other adverse reactions to MPH, or a history of substance abuse disclosed by subject or parent.	24-hour washout
Efron 1997	NR	Yes	No	Fair	NR/NR/125	NR	24-hour washout

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Borcherding 1990	28.30%	Yes	NR	Yes
Casellanos 1997	No	Yes	NR	No
Conners 1980	Unclear	Yes	NIMH and Abbott	
Connor 2000	No	Yes	UMMS Small Grants Project	
Cox 2004	No	Yes	McNeil Consumer and Specialty Pharmaceuticals	Yes
Efron 1997	NO	Yes	NR	Yes

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Efron 1998	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Elia 1990	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Elia 1991	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Elia 1993	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Fitzpatrick 1992	Unclear. No use of "randomized" terminology; No description whatsoever of group assignment	NR	n/a - crossover	No	Yes	Yes	Yes	NR NR NR NR
Gross 1976	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Efron 1998	NR	Yes	No	Fair	NR/NR/102	NR	24-hour washout
Elia 1990	NR	Unclear	Unclear	Fair	NR/NR/31	Evidence of medical or neurologic diseases, or any other Axis I psychiatric disorder (with the exception of conduct disorder or oppositional disorder), specific developmental disorder, or mental retardation.	≥ 3 weeks washout
Elia 1991	NR	Unclear	No	Fair	NR/NR/48	WISC-R full scale IQ < 80; evidence of medical or neurological diseases, or any other Axis I psychiatric disorder, with the exception of conduct disorder, oppositional disorder, mild overanxious disorder, and specific developmental disorders.	NR
Elia 1993	NR	Yes	No	Fair	NR/NR/33	Evidence of medical or neurological disease, or any other Axis I psychiatric disorder, with the exception of conduct disorder or oppositional disorder, and/or specific developmental disorders.	NR
Fitzpatrick 1992	NR	Unclear	Unclear	Poor	NR/NR/19	NR	NR
Gross 1976	NR	No	Unclear	Poor	NR/NR/50	NR	No/No

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Efron 1998	NO	Yes	NR	Yes
Elia 1990	NO	Yes	NR	Yes
Elia 1991	No	Yes	NR	Yes
Elia 1993	No	Yes	NR	No
Fitzpatrick 1992	94.7% naïve to psychotropic medication	Yes	NIMH Grant MH38118, CIBA-GEIGY provided placebo tablets	No
Gross 1976	NR	Yes	NR	Unclear

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
James 2001	NR - order of dose random, but order of drug not clear	NR	n/a - crossover	Yes	Unclear - dose of DEX SR increased part way through study	Yes	Yes	Yes NR NR NR
Kauffman 1981	NR	Yes	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Kemner 2005	NR	NR	No; OROS patients with greater severity of illness at baseline (ADHD-RS 39.9 vs 38.6; p=0.006); adjusted for this difference in the analysis	Yes	NR	No	No	NR Yes NR NR
Kratochvil 2002	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
James 2001	NR/NR	Yes for some efficacy measures; No for CPS and side effects	No	Poor	NR/38/35	WISC-III Full Scale IQ less than 80; presence of a chronic medical or neurological disease including Tourette's disorder, chronic tic disorder, pervasive developments disorders, and mood anxiety disorders requiring current treatment.	No run-in; 3-week washout
Kauffman 1981	NR	Yes	No	Fair	NR/NR/12	No evidence of any neurological disorder, convulsive disorder, mental retardation, metabolic disorder, degenerative neurological disease, or deficit of hearing or sight.	NR/NR
Kemner 2005	NR	NR	NR	Poor	NR/NR/1323	Eating disorders, substance use disorders, comorbid psychiatric conditions other than oppositional defiant disorder; history of seizure, tic disorder, mental retardation, or severe developmental disorder; personal or family history of Tourette's syndrome; previous diagnosis of hyperthyroidism or glaucoma; use of medications contraindicated for coadministration with OROS MPH or atomoxetine; known nonresponse to treatments indicated for ADHD; and occurrence of menarche in girls.	NR/3 days or 5 half-lives
Kratochvil 2002	No/No	No; 10 (4.4%) excluded from analysis due to not having a postbaseline visit	No	Fair	319/NR/228	History of bipolar or psychotic disorders, motor tics or a family history of Tourette syndrome, substance abuse, non-response to a previous trial of MPH (significant residual symptoms after at least 2 weeks of treatment with at least 1.2 mg/kg per day) and serious medical illness.	NR/NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
James 2001	42.8% class naïve	Yes	NR	No, research school setting
Kauffman 1981	NR	Yes	Ciba-Geigy Corp.	Yes
Kemner 2005	No	Yes	McNeil Consumer and Specialty Pharmaceuticals	Yes
Kratochvil 2002	No	Yes	Eli Lilly	Yes

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Lopez 2003	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	Yes NR NR NR
Manos 1999	No, each child's pediatrician determined whether MPH or Adderall was to be used (based on familiarity, as well as whether they wanted a child to receive a single dose or twice-daily dose)	NR	Yes	Yes	No	No	No	NR NR NR NR
Pelham 1987	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Pelham 1990	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Lopez 2003	None	Yes	No	Fair	NR/NR/36	Children with concurrent significant medical or psychiatric illness, or substance use disorder were not permitted in the study.	NR/NR
Manos 1999	NR	Yes	No	Poor	Referred=60/eligible =NR/participated=15 9	NR	NR/NR
Pelham 1987	NR	Unclear	Unclear	Poor	NR/NR/13	NR	NR
Pelham 1990	NR	Unclear	Unclear	Poor	NR/NR/22	NR	NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Lopez 2003	All patients had been stabilized on an equivalent dose of 10 mg twice daily of MPH prior to study entry	Yes	Novartis Pharmaceuticals	Yes
Manos 1999	NR	Yes	NIDA, Maternal and Child Health Program	No
Pelham 1987	NR	Yes	NR	No, Summer Treatment Program
Pelham 1990	NR	Yes	NR	No, Summer Treatment Program+behavior modification intervention

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Pelham 1999a	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Pelham 1999b	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Pelham 2001	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	Yes, NR, Yes (virtually 100%), NR
Pliszka 2000 Faraone 2001	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Pelham 1999a	NR	Unclear	Unclear	Fair	NR/NR/21	No medical history that prohibited them from taking psychostimulant medication or participating in the STP academic or recreational activities.	NR/NR
Pelham 1999b	NR	Yes	No	Fair	NR/NR/25	NR	NR/NR
Pelham 2001	NR/NR	No; 2 patients excluded (2.8%)	No	Fair	NR/NR/70	Presence of any medical condition that would contraindicate the use of stimulant medication; presence of any physical condition or severe learning difficulty that would interfere with participation in the laboratory classroom assessment (WISC IQ < 80); receiving additional medication (beyond MPH) for ADHD; receiving any medication having CNS effects, anticonvulsants, or investigational medications; having reached menarche; and having blood pressure at or aboove the 95th percentile for age and height.	NR/NR
Pliszka 2000 Faraone 2001	No	Yes	No	Fair	73/Unclear/58	DISC criteria for major depression episode, manic episode, or tic disorder; history of psychosis or have signs of psychosis or significantly depressed mood on the mental status examination; BIT composite IQ < 75.	NR/NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Pelham 1999a	24%	Yes	Shire	No; Summer Treatment Program with behavioral training for both children and parents
Pelham 1999b	NR	Yes	Shire	No; Summer Treatment Program with behavioral training for both children and parents
Pelham 2001	No	Yes	Alza	Yes
Pliszka 2000 Faraone 2001	46 (79.3%)	Yes	Shire	Yes

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Sharp 1999	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Simpson 1980	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Stephens 1984	Not randomized; medication was prescribed by each child's physician (method nr)	n/a	n/a - crossover	No	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Sharp 1999	NR	Yes	No	Fair	NR/NR/32	WISC-R Full Scale IQ < 80 and chronic medical or neurological diseases, including Tourette's disorder and chronic tic disorders.	No/Yes
Simpson 1980	No	Yes	No	Fair	NR/NR/12	Excluded severe emotional disorder, organic brain disease, and major medical problems (e.g., sensory impairment, chronic illness, etc.).	NR/NR
Stephens 1984	NR/NR	Unclear	Unclear	Poor	NR/NR/36	NR	NR/NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Sharp 1999	NR	Yes	NR	Unclear
Simpson 1980	No	Yes	NR	Yes
Stephens 1984	Unclear for 25 (69.4%); reported that 11 were taking stimulants at time of study	Yes	NR	Unclear

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Swanson 2004	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	Yes NR NR NR
Tourette's Syndrome Study Group 2002	Yes, computer-generated randomization	Yes, central coordinating center	No, differences in age, proportions of ADHD subtype, ASQ-Teacher scores, and gender	Yes	Yes	Yes	Yes	Yes NR NR NR
van der Meere 1999	NR	NR	Boys and girls were not equally distributed among the groups	No	Yes	Yes	Yes	NR NR NR NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Swanson 2004	NR/NR	Yes	No	Fair	NR/NR/214	Intelligence quotient < 80 or the inability to follow or understand study instructions; pregnancy; a history of seizure or tic disorder; a family history of seizure or Gilles de La Tourette's syndrome; congenital cardiac abnormality, a history of cardiac disease including myocardial infarction within 3 months of study entry, glaucoma, or hyperthyroidism; a history of substance abuse or a caretaker with a history of substance abuse; concurrent chronic or acute illness or other condition that might confound the study rating measures; a documented allergy or intolerance to MPH; the use of an investigational drug within 30 days of study entry; and the use of concomitant medication that could interfere with the assessment of efficacy and safety of the study treatment.	No/No
Tourette's Syndrome Study Group 2002	No/No	Yes	No	Fair	NR/148/136	NR	No/No
van der Meere 1999	NR/NR	Yes	No	Fair	NR/NR/53	NR	NR/NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Swanson 2004	No; only patients BEING treated with MPH	Yes	Celltech	Yes
Tourette's Syndrome Study Group 2002	No	Yes	NIH grant #1R01NS33654	Yes
van der Meere 1999	NR	Yes	Sophia Foundation for Medical Research and Boehringer Ingelheim BV, The Netherlands	Yes

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Whitehouse 1980	NR	NR	No, SR/IR on Overt signs of tension and IR>SR on tension/anxiety	Yes	Yes	Yes	Yes	Yes NR NR NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Whitehouse 1980	None/None	No, 4 (11.8%) excluded from analysis; not stated which groups these 4 were assigned to	Yes, 4 excluded from analysis for: 2 dosage deviations, 1 viral illness, 1 "other reasons"	Fair	NR/NR/34	The presence of glaucoma, epilepsy, severe organic brain damage, mental retardation, cultural deprivation, or psychosis; hypersensitivity to methylphenidate, blindness, deafness, and marked anxiety and tension as the sole manifestations of behavior disorders were excluding factors as well.	Run-in: one month of standard methylphenidate 20 mg (twice daily) prior to study/no washout

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Whitehouse 1980	No	Yes	NR	Yes

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
Wigal 2005	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Wigal 2005	None	No; 12 (5.6%) excluded from analysis; reasons for exclusion unclear	NR	Fair	NR/NR/215	DSM-IV-TR diagnosis of ADHD, predominantly inattentive subtype; current controlled or uncontrolled comorbid psychiatric diagnosis, except ODD, with significant symptoms such as pervasive developmental disorder, post-traumatic stres disorder, psychosis, bipolar illness, severe obsessive-compulsive disorder, severe depression, or severe anxiety disorder; documented history of aggressive behavior serious enough to preclude participation in regular classroom activities, or a DSM-IV-TR diagnosis of conduct disorder; documented allergies, adverse reactions, or intolerance of stimulants, including MAS XR, atomoxetine, or tricyclic antidepressants, or a history of failure to respond clinically to adequate doses of these medications; history of suspected substance abuse of drug abuse (excluding nicotine) or living with someone with such history of suspicion; taking any prohibited medicationincluding antideprssants, antipsychotics, neuroleptics, anxiolytics, and anticonvulsants; or history of seizure during the past 2 years, a tic disorder, or a family history of Tourette's Disorder.	4-day single-blind placebo lead-in period/washout of previous medications, but no details provided

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Wigal 2005	No	Yes	In part by NIMH award MH02042 and a grant from Shire	Yes

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Wolraich 2001	Yes	Yes	Small differences (NS) : proportions with comorbidities, prior MPH IR use, inattentive vs combined ADHD	Yes	Yes	Yes	Yes	Yes NR NR NR
Steele 2006	Yes; Site randomization lists	Yes	Yes	Yes	N	N	Y	Y/NR/Y/NR % of subjects who missed any dose during the trial was higher with IR-MPH (84%) than OROS-MPH (56%).

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Wolraich 2001	No/No	Yes	No	Fair	500/405/312 randomized	Acute or serious chronic disease, were hypersensitive to methylphenidate, were having significant adverse experiences from methyphenidate, or were taking a medication that would interfere with the safe administration of methylphenidate; patients with glaucoma, Tourette's syndrome, an ongoing seizure disorder, or a psychotic disorder, as were girls who had reached menarche.	NR/NR
Steele 2006	N/N	Yes	NR	Poor	187/147/145	Known MPH non-responders, hypersensitivity, or adversely affected by methylphenidate; concomitant use of contraindicated medication likely to interfere with the safe administration of study medication; marked anxiety, tension, aggression/agitation; glaucoma; ongoing seizure disorder; psychotic disorder; diagnosis or family history of Tourette's disorder; bipolar disorder; suspected mental retardation or significant learning disorder; medication/alcohol abuse/dependence by either the child or parent; history of, or current eating disorder; severe gastrointestinal narrowing; inability to swallow study medications; and any serious/unstable medical illness.	Y/Y 3 day washout at study commencement of any drug for ADHD

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Wolraich 2001	No	Yes	Alza	Yes
Steele 2006	N	Y	Janssen-Ortho Inc., Canada	Yes

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Findling 2006	Unclear; randomized in a ratio of 3:3:1 (p 452)	NR	Yes, for tx arms; O/D component of IOWA Conners' Scale lower (better) in placebo group compared to either tx group	Yes	NR	Yes	Yes	Y NR NR NR
Gau 2006	NR	NR	Yes	Yes	Partial; parent reporters knew which medication, teachers reporters did not	NR	N	Y Y Y N IR MPH group had less adherence than the OROS MPH group (p < 0.0001); report states this did not change the results

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Findling 2006	N/N; Placebo group had a high % of study withdrawal compared to the two tx arms; withdrawal data on page 454.	Yes; stated in results, no data provided	Yes; 6 based on clinician's judgment (5 in placebo; 1 in MPH-IR)	Fair	346/327/318	Female who had reached menarche, co-morbid psychiatric disorder requiring medication, history of seizure, tic disorder, or a family history of Tourette's disorder, IQ test <80, or functioning at a level of intelligence indicative of an IQ <80, the use of unapproved medication(s), use of an investigational product within 30 days prior to study entry, concurrent chronic or acute illness, disability, or medication, that might confound the results of rating tests, diagnosed with hyperthyroidism, glaucoma, or eating disorder, current substance abuse disorder or living with someone with a current substance abuse disorder, demonstrated lack of response to methylphenidate	NR/NR; children were taking pre-study methylphenidate (MPH) medication at baseline
Gau 2006	N/N	Y	N	Fair	NR/NR/64	Significant gastrointestinal problems, a history of hypertension, known hypersensitivity to MPH, or a co-existing medical condition or concurrent medication (such as monoamine oxidase inhibitors, and medicines used to treat depression, prevent seizure, or prevent blood clots) likely to interfere with the safe administration of MPH. Glaucoma, Tourette's Syndrome, an active seizure disorder, or a psychotic disorder, girls who had reached menarche.	NR/Y washed out MPH for 5-7 days

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Findling 2006	No	Yes	Celltech Americas, Inc	Yes
Gau 2006	NR	Yes	Jansessen-Cilag, Taiwan.	Unclear; 64 participants from one medical center in Taipei

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

	Internal Validity							
Study	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition, adherence**
McCracken 2003	Unclear; Latin square design;	Y; randomization schedules generated by the sponsor and distributed to the onsite pharmacist	n/a - crossover	Yes	Yes; states double blind but no details	Yes; states double blind but no details	Yes; states double blind but no details	Y Y Y N
Prasad 2007	NR	NR	No, higher proportion with inattentive subtype in Atomoxetine gro (11.5%) vs control (3.1%)	Yes	No	No	No	Y NR NR NR

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
McCracken 2003	N/N	Yes	N	Fair	NR/51/47	Comorbid psychiatric conditions including psychosis, pervasive developmental disorder, bipolar disorder; severe obsessive-compulsive disorder, severe depressive or anxiety disorder (severe defined as any comorbid disorder with impairment necessitating concurrent treatment of any type); a clinically significant medical condition (e.g., seizure disorder, hypertension, abnormal laboratory test result); need for ongoing medical treatment; intolerance of psycho stimulants; history of nonresponse to Adderall; or history of a tic disorder.	NR/Y 1 week washout
Prasad 2007	Y (discontinuation from trial 25% atomoxetine, 6% control N	Unclear - modified ITT stated, appears only 75% of atomoxetine grp included inanalysis, while 94% of control grp	Y;N	Poor	NR/208/201	Weight < 20 Kg, history of bipolar disorder, pschotic disorders, PDD, seizure disorders, alcohol/drug abuse, significant prior/current medical conditions, at risk of suicaide, taking medications that may interfere with study outcomes.	Y/N 3-28 days

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
McCracken 2003	N	Yes	Supported by a grant from Shire Pharmaceutical Development Inc.	Unclear
Prasad 2007	No	Yes	Eli Lilly	Relevant to outpatient centers in UK, patients without other psycholoigical ormedical conditions.

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Internal Validity

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition, adherence
Silva 2005	Unclear; For counterbalancing, 10 crossover treatment sequences used; Williams design to control for effects of treatment order and relative position.	NR	NR; only data on entire study group	Yes	Yes	No; those dispensing medication not blinded	Yes; although states some might have known what they were taking	N N N N
Sangal 2006	NR	NR	n/a - crossover; reported no differences at baseline	Yes	Yes; states double blind but no details	Yes; states double blind but no details	Yes; states double blind but no details	Y Y Y N

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

					External Validity		
Study	**Loss to followup: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**
Silva 2005	N/N	Unclear	N	Fair	NR/NR/54	Functioning at an IQ level of 80 or below, based on the investigator's clinical judgment; diagnosed with Tourette syndrome or a tic disorder; history of a seizure disorder; or unable to understand or comply with study instructions. Significant concurrent medical or psychiatric illness or substance-abuse disorder. A history of sensitivity to MPH, those with a history of substance abuse or dependence, those currently taking atomoxetine, and those who had taken, were currently taking, or were planning to take any investigational drug within 30 days of the study start date. Postmenarchal females.	NR/NR; 12 hour post dose observations
Sangal 2006	N/N	NO	Y; 35 due to low actigraphy scores or equipment malfunction	Poor	107/85/85 (75 completed) Only 50 cases analyzed due to low actigraphy scores	Inconsistent adherence to 'bed-time' as scheduled; serious medical illness, a history of symptoms suggestive of a primary sleep disorder-such as as obstructive sleep apnea (OSA) (e.g., habitual snoring), periodic limb movement disorder (PLMD, eg, kicking movements during sleep), or insufficient sleep syndrome (e.g., voluntary sleep restriction resulting in sleep duration habitually significantly shorter than expected age norms}--that could potentially result in a daytime symptom constellation similar to ADHD, and abnormal laboratory values or electrocardiogram (ECG) readings.	Yes - 22 of 107 (21%) excluded during screening/Y Phase II of study: 10-20 day study drug washout

Evidence Table 4. Quality assessment of head to head trials in children with ADHD

Study	Class naïve patients only	Control group standard of care	Funding	Relevance
Silva 2005	N; Patients were instructed to continue taking their regularly prescribed medication for 5 days of the week; administered study drug on Saturdays	Yes	Novartis Pharmaceuticals Corporation	N; Saturday school - 12 hour observation post tx
Sangal 2006	N (mixed)	Yes	Sponsored by Eli Lilly; data were analyzed by statisticians at Eli Lilly.	Unclear

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Atomoxetine			
Kelsey 2004	RCT, DB	Children 6 to 12 years of age who met Diagnostic and Statistical Manual of Mental Disorders (4th ed.) criteria for ADHD, as assessed in clinical interviews and confirmed in parent interviews using the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged children-Present and Lifetime Version. All patients were required to meet a symptom severity threshold, with a symptom severity score at least 1.5 SDs above age and gender normative values, as assessed with the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHD RS), for the total score or either of the inattentive or hyperactive/impulsive subscales.	Oppositional/defiant disorder: 37.6% of atomoxetine group; 29.7% of placebo group Conduct disorder: 5.3% of atomoxetine group; 1% of placebo group

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Atomoxetine				
Kelsey 2004	randomized to receive atomoxetine or placebo, dosed once daily in the mornings. Patients in atomoxetine group were given 0.8mg/kg/day for 3 days, with the dose increasing to 1.2mg/kg/day. Dose never to exceed 120 mg/kg/day. This was a 8 week treatment study.	5 day washout period.	NR/NR	ADHD RS, Daily parent Ratings of Evening and Morning Behavior Revised (DPREMB-R), Conners Global Index; Parent-Evening (GIPE), CGI ADHD-S.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Atomoxetine				
Kelsey 2004	Children aged 6-12 years/71% enrolled were male/ ethnicity NR.	ADHD Subtypes Combined: 37.6% of atomoxetine, 67.2 % of placebo Hyperactive/impulsive: 3.8% atomoxetine, 3.1% of placebo Inattentive: 26.3% of atomoxetine, 29.7% of placebo	260 screened/197eligible/197 enrolled	Atomoxetine: 26 withdrawn 4 lost to fu 107 analyzed Placebo: 17 withdrawn 3 lost to fu 47 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Atomoxetine		
Kelsey 2004	Source: Atomoxetine: baseline vs endpoint vs change; Placebo: baseline, endpoint, change; 95%CI for Difference From Placebo ADHD RS (atomoxetine: n=126; placebo: n=60) Total score: 42.1 (9.2) vs 25.3 (14.3) vs -16.7 (14.5)*; 42.3 (7.1) vs 35.2 -12.3) vs -7.0 (10.8); -13.8, -5.9 Inattentive subscore: 22.6 (3.9) vs 14.3 (7.6) vs -8.3 (8.0)*; 23.0 (3.4) vs 19.0 (6.5) vs -4.1 (6.1); -6.7, -2.3 Hyperactive/impulsive subscore: 19.5 (6.8) vs 11.0 (7.7) vs -8.5 (7.5)*; 19.2 (5.9) vs 16.3 (7.5) vs-2.9 (5.8); -7.5, -3.4 DPREMB-R (atomoxetine: n= 113; placebo: n=50) Total Score: 17.1 (7.2) vs 9.4(6.3) vs -7.7 (5.8); 15.4 (6.7) vs 10.9 (6.1) vs -4.5 (5.3) vs -4.0, -0.9 Evening subscore: problems with homework/tasks: 1.8(0.8) vs 1.0(0.7) vs -0.8 (0.7)*; 1.6(o.8) vs 1.2 (0.7) vs -0.4 (0.6) ; -0.4,-0.1 difficulty sitting through dinner: 1.4(0.8) vs 0.8(0.7) vs -0.6(0.7); 1.3(0.8) vs 0.8(0.7);-0.5 (0.6); -0.3, 0.1 Difficulty playing quietly: 1.7(0.9) vs 0.9 (0.7) -0.9(0.7)*; 1.5(0.8) vs 1.1 (0.8) vs -0.4 (0.7) ; -0.6, -0.2) Inattentive and distractible: 1.9(0.7) vs 1.1 (0.7) vs -0.9 (0.7)*; 1.8 (0.7) vs 1.3 (0.7) vs -0.5(0.6) ; -0.4, -0.1 Difficulty transitioning: 1.6(0.7) vs 0.9(0.6) vs -0.7(0.7); 1.5(0.7) vs 1.1(0.6) vs -0.5(0.7); -0.4,-0.1 Arguing or struggling: 1.7(0.8) vs 1.0(0.7) vs-0.79).7); 1.6(0.8) vs 1.1(0.8) vs -0.5(0.7); -0.4,0.0 Difficulty settling at bedtime: 1.7(0.8) vs 0.8(0.7) vs -0.8(0.7)*; 1.5(0.8) vs 1.0(0.7) vs-0.5, -0.7); -0.5,-0.1 Difficulty falling asleep: 1.2(0.7) vs 0.6(0.7) vs -0.6(0.7); 1.1(0.9) vs0.7(0.7) vs -0.4(0.7); -0.3, 0.0 Morning subscore Difficulty getting out of bed: 1.2(90.8) vs 0.7(0.7) vs -0.5(0.6); 1.3 (0.7) vs 1.0(0.6) vs -0.3(0.6); -0.4, -0.0 Difficulty getting ready: 1.5(90.7) vs 0.9(0.7) vs -0.6(0.6)*; 1.3(0.7) vs 1.0(0.6) vs-0.3(0.6); -0.4, -0.0 Arguing or struggling: 1.3(0.8) vs 0.7(0.7) vs -0.6(0.7)*; 1.2 (0.8) vs 0.9(0.7) vs -0.3(0.7); -.4, -0.0 Conners GIPE (atomoxetine: n=127, placebo: n=60) Total Score: 20.1(6.1) vs 13.3(7.3) vs -6.8(6.8)*; 20.1(5.5) vs 16.9(7.3) vs -3,2(6.9); -5.7, -1.8 Restless-impulsive subscale total: 15.8(4.2) vs 10.1(5.6) vs -5.7(5.3)8; 15.5(4.1) vs 13.5(5.3) vs-2.0(5.2); -5.2,-2.1 Emotional liability subscale total: 4.3(2.6) vs 3.2(2.5) vs -1.2(2.4)*; 4.6(2.4) vs 3.4(2.7) vs-1.3(2.4); -0.7, 0.6 CGI-ADHD-S (atomoxetine: n=126; placebo: n=60): 5.0(0.8) vs 3.5(1.3) vs -1.6(1.4)*; 5.0(0.8) vs -0.7(1.1) ; -1.2; 5 * p<.05	measuring vital signs, ECK's, open-ended questioning about negative physical symptoms and laboratory tests.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Atomoxetine			
Kelsey 2004	**Event: Atomoxetine (n=131) vs Placebo (n=63)** Decreased appetite: 23 (17.6)* vs 4(6.3) Abdominal Pain: 20(15.3) vs 4(6.3) Nausea: 15(11.5) vs 5(7.9) Somnolence: 19(14.5)* vs 1(1.6) Headache: 9(6.9) vs9(14.3) Fatigue: 13(9.)* vs 1 (1.6) Dyspepsia: 8(6.1) vs 1(1.6) Vomiting: 8(6.1) vs 1(1.6) Diarrhea: 2(1.5) vs 4 (6.3) *=p<.05	Atomoxetine: 6 Placebo: 1	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Spencer 2002	RCT DB	Patients were at least 7 years of age but less than 13 years of age at the initial visit and were determined to be of normal intelligence based on the Weschler Intelligence Scale for Children-Third Edition (WISC-III). Patients were required to meet DSM-IV diagnostic criteria for ADHD, as assessed by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia, and have a score on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHD RS) at least 1.5 standard deviations above the age and gender norms for their diagnostic subtype (primarily inattentive or primarily hyperactive/impulsive) or the total score for the combined subtype.	Atomoxetine: Oppositional defiant disorder-53(41.1%) Elimination disorders-10(7.8%) Phobias-16(12.4%); Dysthymia-7(5.4) Generalized anxiety disorder-4(3.1) Major depressive disorder-4(3.1) Placebo: Oppositional defiant disorder-45(36.3%) Elimination disorders-15(12.1%) Phobias-13(10.5%); Dysthymia-5(4.0) Generalized anxiety disorder-3(2.4) Major depressive disorder-4(3.2)
Kaplan 2004 U.S. ODD/ADHD subset analysis of Spencer 2002	DB, PCT	Patients were 7-13 years and met diagnostic criteria for ADHD as defined by DSM-IV and met diagnostic criteria for ODD as characterised by DICA-IV and confirmed by clinical assessment according to the DSM-IV criteria. All children had an IQ in the normal range, as measured by the WISC-III.	All patients (n=98) in this subset had ODD

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Spencer 2002	atomoxetine 2mg/kg/day or a total 90mg/day based on therapeutic response and tolerability for 9 weeks	2 weeks		ADHD Rating Scale (ADHD RS) rated by trained clinicians during every visit based on an interview with the parent and child. Responders are defined as having a minimum 25% reduction in ADHD RS total score and also the change in Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) and Conners Parent Rating Scale-Revised: Short Form (CPRS-R:S)
Kaplan 2004 U.S. ODD/ADHD subset analysis of Spencer 2002	see Spencer 2002 above Atomooxetine (n=53) Placebo (n=45) Max dose was the lower of either 2 mg/kg/d or 90 mg/d Mean total daily dose: 55.3 mg (SD = 19.0) Treatment as follows: 2 week medication washout (visits 1-3), then a 9-week DB treatment phase (visits 3-12) and then a 1 week single blind discontinuation phase (visits 12-13).	NR / 2-week washout	NR	Primary efficacy measure: ADHD RS - IV-Parent Version, an 18-item scale. The Inattention and Hyperactivity/Impulsivity subscales were also computed. Secondary measures: Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) and the Clinical Global Impressions of ADHD Severity (CGI-ADHD-S).

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Spencer 2002	Atomoxetine: Age- mean=9.7 Gender- 98(76%) male Placebo: Age- mean=10 Gender- 103(83%) male Race: NR	Mean IQ: Atomoxetine=103, placebo=106.9, p=0.021	409 screened/ 291 eligible/ 253 enrolled	59 withdrawn/ 0 lost to fu/ 253 analyzed
Kaplan 2004 U.S. ODD/ADHD subset analysis of Spencer 2002	Mean age: 9.98 years 79.6% male Ethnicity: NR	Mean WISC-III Full scale IQ: 104.9 Mean ADHD-RS Total score: 42.1 ADHD-RS Inattentive subscale: 22.0 ADHD Hyperactive/Impulsive subscale:20.0 CGI-ADHD-S: 5.15 Conners Parents RS: ADHD Index: atomoxetine 27.3 vs placebo 28.6	see above Spencer 2002	in this subset, 24 / NR / 98

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Spencer 2002	*atomoxetine: placebo= mean-study1, p value; mean-study2, p value* ADHD RS Total= -15.6:-5.5, p<0.001; -14.4:-5.9, p<0.001 ADHD RS sub-- Inattentive= -7.5:-3.0, p<0.001; -7.6:-3.0, p<0.001 Hyperactivity/impulsive= -8.0:-2.5, p<0.001; -6.9:-2.9, p=0.002 CGI-ADHD-severity= -1.2:-0.5, p=0.003; -1.5:-0.7, p=0.001 CPRS-ADHD Index= -5.7:-2.6, p=0.023; -8.8:-2.1, p<0.001 *ADHD RS total score deduction percentage* Study1-- atomoxetine: placebo= 64.1%: 24.6%, p<0.001 Study2-- atomoxetine: placebo= 58.7%: 40.0%, p=0.048	vital sign assessment NR for symptoms
Kaplan 2004 U.S. ODD/ADHD subset analysis of Spencer 2002	Mean change in scores, baseline to endpoint, atomoxetine vs placebo: ADHD RS Total : -17.0 vs -7.5, p<0.001 (effect size=0.72) Inattentive subscale: -8.7 vs -3.9, p<0.001 (effect size=0.71) Hyperactive/Impulsive subscale: -8.3 vs -3.6, p=0.002 (effect size=0.66) CGI-ADHD-Severity: -1.5 vs -0.7, p=0.003 Conners' Parent rating scale and subscale scores: ADHD Index: -7.7 vs -3.2, p=0.005 Cognitive: -4.1 vs -1.6, p=0.006 Hyperactive: -4.3 vs-1.3, p=0.003 Oppositional: -2.4 vs -1.8 p=0.796	See Spencer 2002

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Spencer 2002	*Atomoxetine: placebo* Headache, abdominal pain, rhinitis, pharyngitis, vomiting, cough increased, nervousness, somnolence, nausea: NS Decreased appetite= 21.7%: 7%, p<0.05 Systolic blood pressure, temperature: NS Diastolic blood pressure= 9.6:8.3, p=0.008 Heart rate, bmp=9.2:1.5, p<0.001	atomoxetine: total withdrawals=27 due to adverse events=6(4.7%) placebo: total withdrawals=32 due to adverse events=3(2.4%)	
Kaplan 2004 U.S. ODD/ADHD subset analysis of Spencer 2002	AEs with significant differences, atomoxetine vs placebo: Decreased Appetite: 18.9% vs 2.2%, p<0.01 Emotional Lability: 11.3% vs 0.0%, p=0.03 Other AEs: atomoxetine vs placebo: Abdominal pain: 28.3% vs 22.2%, p=0.643 Headache: 28.3% vs 28.9%, p>0.99 Rhinitis: 24.5% vs 35.6%, p=0.271 Pharyngitis: 18.9% vs 15.6%, p=0.791 Nausea: 15.1% vs 11.1%, p=0.766 Nervousness: 15.1% vs 6.7%, p=0.271 Vomiting: 15.1% vs 15.6%, p>0.99 Cough increased: 11.3% vs 8.9%, p=0.75 Diarrhea: 11.3% vs 8.9%, p=0.75 Somnolence: 11.3% vs 6.7%, p=0.501 Fever: 7.5% vs 13.3%, p=0.505	24 (12 per group) ; 5 (3 in atomoxetine and 2 in placebo)	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Michelson 2002	RCT, DB, parallel, setting:NR	Children and adolescents, 6-16 years of age, who met DSM-IV criteria for ADHD, as assessed by clinical interview and confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)(7), were eligible to participate. All patients were required to meet a symptom severity threshold: a score at least 1.5 standard deviations above age and gender norms as assessed by the investigator-administered and -scored parent version of the ADHD Rating Scale -IV. Comorbid psychiatric conditions were assessed clinically and with the K-SADS-PL.	Co-morbidity trait: placebo n vs atomoxetine n Oppositional defiant disorder: 21.2% vs 18.8% Depression: 1.2% vs 2.4% Generalized Anxiety Disorder: 0% vs 1.2% Specific Phobia: 2.4% vs 3.5%.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Michelson 2002	Patients in Atomoxetine treatment group began at 0.5mg/kg/day for 3 days, followed by 0.75mg/kg/day for the remainder of the first week. The daily dose was then increased to 1.0mg/kg/day. This was a 6 week treatment.	NR	5 day washout	Primary outcome measure was total score on ADHD Rating Scale-IV. Other outcome assessment tools included: Connor's Parent Rating Scale-Revised: Short Form, Connor's Teacher Rating Scale-Revised: Short Form, CGI severity score, 13-item parent-rated diary assessing efficacy rates with a Likert scale. Laboratory exams were also conducted at baseline and endpoint.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Michelson 2002	children aged 6-16 years/ 70.6% male, 29.4 female/ ethnicity NR.	**ADHD subtypes** mixed: 60% of placebo, 55.3% of atomoxetine group hyperactive/impulsive: 0% of placebo, 3.5% of atomoxetine group inattentive: 40% of placebo, 41.2 of atomoxetine	NR/ 171/170	3%/NR/ 170

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Michelson 2002	Placebo(N=83) baseline mean vs mean of change from baseline; Atomoxetine(N=84) baseline mean vs mean of change from baseline; analysis of variance p-value ADHA rating scale-IV: 36.7 vs -5; 37.6 vs -12.8; p=<0.001 Inattentive symptoms: 21.4 vs -2.9; 21.9 vs -7.1; p=<0.001; Hyperactive/impulsive score: 15.3 vs -2.1; 15.7 vs -5.7; p=<0.001 CGI severity score: 4.6 vs -0.5; 4.7 vs -1.2; p=<0.001 Conners Parent rating scale: 26.5 vs -2.4; 27 vs -7.6; p=<0.001 Connors Teacher rating scale: 21.6 vs -1.6; 21.5 vs -5.1; p=0.02 Parent ratings of offspring behavior problems with homework/tasks: 1.8 vs -0.3; 1.8 vs-0.5; p=0.49 sitting thorough dinner: 1.0 vs -0.1; 1.3 vs-0.4; p=0.18 difficulty playing quietly: 1.4 vs -0.3; 1.5 vs -0.5; p=0.15 inattentive and distractible: 1.8 vs -0.3; 1.9 vs -0.7; p=.003 arguing or struggling-evening: 1.4 vs -0.3; 1.5 vs -0.4; p=0.89 irritability-evening: 1.3 vs -0.3; 1.6 vs -0.6; p=0.43 difficulty with transitions: 1.5 vs -0.3; 1.6 vs -0.6; p=0.13 difficulty settling at bedtime: 1.7 vs -0.3; 1.8 vs -0.6; p=0.30 difficulty falling asleep: 1.6 vs -0.4; 1.8 vs -0.6; p=0.30 difficulty getting out of bed: 1.1 vs -0.2; 1.1 vs -0.3; p=0.53 difficulty getting ready: 1.4 vs -0.2; 1.1 vs -0.3; p=0.53 arguing or struggling-morning: 1.0 vs -0.2; 1.0 vs-0.2; p=0.63 irritability-morning: 0.8 vs -0.1; 0.8 vs -0.1; p=0.74	reports from patient/parent of negative physical symptoms

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Michelson 2002	**Event: Placebo: N, % vs Atomoxetine: N, %; Fisher's Exact p** Headache: 15, 17.6% vs 17, 20.0%; 0.85 Rhinitis: 18, 21.2% vs 14, 16.5%; 0.56 Decreased appetite: 5, 5.9% vs 17, 20.0%; 0.02 Abdominal pain: 7, 8.2% vs 14, 16.5%; 0.17 Pharyngitis: 13; 15.3% vs 6, 7.1%; 0.15 Increased coughing: 11, 12.9% vs 6, 7.1%; 0.31 Somnolence: 6, 7.1%; 9, 10.6; 0.59 Vomiting: 1, 1.2% vs 13, 15.3%; 0.001 Nausea: 2, 2.4% vs 10, 11.8%; 0.04 Asthenia: 1, 1.2%, 9, 10.6%; 0.02 Emotional lability: 4, 4.7%, 6, 7.1%; 0.50 Rash: 4, 4.7%; 5, 7.1; 0.75 Accidental injury: 4, 4.7%; 5, 5.9%; 0.99 Fever: 3, 3.5%; 6,7.1%; 0.50 Dyspepsia: 0, 0%; 8, 9.4%; 0.007 Dizziness: 0, 0%; 5,5.9%; 0.06	3 subjects/2 subjects	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Michelson 2001 Good quality	RCT, DB, parallel, Setting: 13 outpatient sites in the United States, Patient visits were weekly for the first 4 weeks of study, and bi-weekly for the remaining 4 weeks of study.	Patients aged 8-18 years of age, meeting the DSM-IV criteria for ADHD by clinical assessment and confirmed by structured interview (behavioral module of the Kiddie Schedule for Affective disorders and Schizophrenia for School-Aged Children-Present and Lifetime Versions).	ADHD subtypes: mixed: 67%, hyper-active/impulsive: 2%, inattentive: 31%, unspecified: less than 1%. Co-morbid conditions: oppositional/defiant disorder: 38%, depression: less than 1%, generalized anxiety disorder: less than 1%.
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	RCT, DB	51 girls who met the diagnostic criteria for ADHD based on DSM-IV and as assessed by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia and with normal intelligence based on WISC, 3rd edition. Exclusionary criteria: poor metabolism of cytochrome P450 2D6 isoenzyme, weight <25kg at initial visit; a documented history of bipolar I or II or of psychosis; history of organic brain disease or a seizure disorder; currently taking psychotropic medicine; history of alcohol or drug abuse in past 3 months; positive screening for drugs of abuse; or significant previous or current medical conditions (eg, HIV positive, surgically corrected congenital heart defects, leukemia in remission).	Oppositional/defiant disorder: 38.5% Phobias: 13.5%

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Michelson 2001 Good quality	Placebo Atomoxetine doses randomized to .5mg/kg/day, 1.2mg/kg/day, or 1.8mg/kg/day. Amounts were divided equally to patients to 2 daily doses, for 4 weeks.	12-18 day evaluation and washout period. Sizes NR.	NR	ADHD RS (semistructured interview with patient's caregiver), Conner's Parent Rating Scale: revised: short-form, Clinical Global Impressions of Severity. Affective symptoms were assessed using Children's Depression Rating Scale. Social and family functioning assessed with Child health Questionnaire. Binary measure assessed with Fisher's exact test. Dose-response relationships assessed with Cochran-Armitage trend test.
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	Randomized to receive atomoxetine or placebo, dosed in the morning and in the late afternoon/early evening. 9-weeks duration. Atomoxetine was titrated up to a maximum daily dose of 2.0 mg/kg per day (max. total daily dose = 90 mg/day)	2-week washout, screening, and assessment period	No	Primary efficacy measure: ADHD Rating Scale - IV-Parent Version (ADHD RS), an 18-item scale. Secondary measures: Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) and the Clinical Global Impressions of ADHD Severity (CGI-ADHD-S). The ADHD RS was given at every weekly visit (it assessed the severity of symptoms in the previous week) to parents.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Michelson 2001 Good quality	mean age 11.2 male: 71% female: 29% ethnicity NR.		381/297/297	16 (16.5%) withdrawn/ 10 (3.3%) lost to fu/292 . Placebo n=83, ATMX .05 n=43; ATMX 1.2 n=84; ATMX 1.8 n=82.
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	Mean age in years: 9.66 Males = 0% Ethnicity = NR	Diagnostic subtypes: -Inattentive = 21.2% -Hyperactive/impulsive = 0% -Combined = 78.8% Mean Scores: WISC Full Scale IQ = 105.2 ADHD RS Total T-Score = 88.9 ADHD RS (Total) = 38.2 ADHD RS Inattentive subscale = 21.4 ADHD RS Hyperactive/Impulsive subscale = 16.7 CPRS-R ADHD index = 26.9 CGI-ADHD-S = 4.8	NR/NR/291 (52 total girls)	1/NR/51

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Michelson 2001 Good quality	Placebo vs Atomoxetine 0.5 mg/kg (n=43) vs Atomoxetine 1.2 mg/kg (n=84) vs Atomoxetine 1.8 mg/kg (n=82) (all with 95% CI for difference from placebo ADHD RS Total: -5.8 vs -9.9 (-8.9, 0.9) vs -13.6 (-12.1, -4.0, p<0.05) vs -13.5 (-11.9, -3.7; p<0.05) Inattention subscale: -2.5 vs -5.1 (-5.2, 0.3) vs -7.0 (-6.8, -2.2, p<0.05) vs -6.8 (-6.6, -2.0, p<0.05) Hyper/Imp Subscale: -3.2 vs -4.8 (-4.1, 1.0) vs -6.6 (-5.6, -1.4, p<0.05) vs -6.7 (-5.7, -1.4, p<0.05) CPRS-R ADHD Index: -1.5 vs -7.2 (-9.2, -2.1, p<0.05) vs -8.9 (-10.3, -4.5, p<0.05) vs -8.8 (-10.0, -4.2, p<0.05) Hyperactive Subscale: -1.1 vs -4.1 (-4.5, -1.2, p<0.05) vs -4.1 (-4.4, -1.6, p<0.05) vs -4.3 (-4.5, -1.8, p<0.05) Cognitive Subscale: -0.4 vs -2.4 (-4.7, -0.6, p<0.05) vs -4.8 (-6.0, -2.6, p<0.05) vs -4.6 (-5.8, -2.4, p<0.05) Oppositional Subscale: 1.1 vs -0.3 (-4.0, 1.6) vs -1.5 (-5.0, -0.5, p<0.05) vs -2.0 (-5.2, -0.7, p<0.05) CDRS-R: 1.1 vs -0.3 (-4.0, 1.6) vs -1.5 (-5.0, -0.5, p<0.05) vs -2.0 (-5.2, -0.7, p<0.05) CHQ Physical: 0.4 vs -.6 (-4.1, 0.25 vs -1.1 (-4.0, 1.4) vs -2.0 (-4.9, 0.5) Psychosocial Summary Score Behavior: -0.4 vs 8.2 (1.7, 15.7, p<0.05) vs 13.0 (7.9, 19.5, p<0.05), 16.3 (10.9, 22.4, p<0.05) Family activity: 0.7 vs 8.7 (-0.6, 17.9) vs 14.6 (6.3, 21.5, p<0.05), 15.2 (7.3, 22.2, p<0.05) Parent impact-emotional: 3.0 vs 5.7 (-6.1, 11.1) vs10.1 (-0.3, 14.0) vs 11.0 (1.2, 15.2, p<0.05) Child emotional: -4.4 s 7.6 (-3.2, 26.1) vs 7.9 (-0.4, 23.9) vs 15.9 (7.7, 31.6, p<0.05) Child mental health: -1.9 vs 7.7 (3.7, 15.1, p<0.05) vs 4.5 (1.6, 11.1, p<0.05) vs 8.9 (5.6, 15.0, p<0.05) Child self-esteem: 1.4 vs 1.4 (-4.7, 9.3) vs 5.4 (-3, 11.9, p<0.05) vs 8.4 (4.2, 15.6, p<0.05)	The following vital signs were tracked throughout the study: Blood Pressure Systolic, Diastolic, Pulse, Weight. Patient self-reports of negative health symptoms were noted at appointments.
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	ADHD RS Total score decrease - Atomoxetine-treated vs. placebo: -15.8 vs. -5.8, p=0.002 ADHD RS Inattentive subscale decrease - Atomoxetine-treated vs. placebo: -8.8 vs. -3.4, p=0.001 ADHD RS Hyperactivity/Impulsive subscale decrease - Atomoxetine-treated vs. placebo: -7.0 vs. -2.3 p=0.006 A visit-wise analysis found that atomoxetine-treated patients experienced signficant efficacy over placebo that was evident every week of treatment (p<0.05 for Weeks 1,2,5, and 6; p<0.01 for Weeks 3,4,7,8, and 9) CPRS-R ADHD Index scores decrease - Atomoxetine-treated vs. placebo: -10.3 vs. -1.0, p<0.001 CGI-ADHD-S score decrease - Atomoxetine-treated vs. placebo: -1.5 vs. -0.6, p<0.001	AE's reported by patients

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Michelson 2001 Good quality	**Symptom: placebo vs ATMX .5mg/kg/day vs ATMX 1.2mg/kg/day vs ATMX 1.8 mg/kg/day.** Headache: 19 vs 11 vs 20 vs 20. Rhinitis: 18 vs 7 vs 10 vs 12. Abdominal pain: 9 vs 5 vs 12 vs 12. Pharyngitis: 12 vs 4 vs 9 vs 9. Anorexia: 4 vs 3 vs 10 vs 10. Vomiting: 5 vs 3 vs 6 vs 9. Cough increased: 4 vs 6 vs 6 vs 7. Somnolence: 3 vs 2 vs 6 vs 9. Insomnia: 5 vs 4 vs 5 vs 4. Rash: 3 vs 3 vs 5 vs 7. Nausea: 5 vs 2 vs 6 vs 4. Nervousness: 4 vs 3 vs 5 vs 5. Fever: 5 vs 1 vs 7 vs 3. Pain: 5 vs 4 vs 2 vs 5. Accidental injury: 7 vs 1 vs 3 vs 3. Asthenia: 4 vs 3 vs 2 vs 4. Infection: 1 vs 0 vs 5 vs 6. Dizziness: 1 vs 4 vs 2 vs 4. Diarrhea: 5 vs 0 vs 4 vs 0. Depression: 5 vs 1 vs 0 vs 2. Pruritus: 0 vs 0 vs 1 vs.5	Less than 1% of withdrawals were due to adverse events.	
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	Rhinitis: Atom.(n=31)* 25.8%; Placebo(n=21)* 38.1% Abdominal pain: 29.0%; 14.3% Headache: 25.8%; 14.3% Pharyngitis: 19.4%; 19.0% Decreased appetite: 19.4%; 19.0% Vomiting: 19.4%; 0% Cough increased: 16.1%; 4.8% Nervousness: 6.5%; 14.3% Somnolence: 6.5%; 14.3% Nausea: 6.5%; 14.3% Emotional lability: 3.2%; 14.3% Fever: 9.7%; 4.8% Insomnia: 3.2%; 9.5% Diarrhea: 3.2%; 4.8% Dizziness: 3.2%; 4.8% *(no statistically significant differences between these two	3 withdrawals/ 2 due to AE's	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Michelson 2004	RCT, DB Setting: 33 academic investigative centers in Europe (24 centers), Israel (two centers), South Africa (four centers), and Australia (three centers)	Patients aged 6 to 15 years who met DSM-IV criteria for ADHD assessed by clinical history and confirmed by a structured interview (schedule for affective disorders and schizophrenia for school-age children-present and life-time version [K-SADS-PL]) and whose symptom severity was at least 1.5 SD above US age and gender norms	Atomoxetine: n=292 Comorbid condition oppositional defiant disorder: 42.1% depression: 2.1% generalized anxiety disorder: 2.7% Placebo: n=124 Comorbid condition oppositional defiant disorder: 45.2% depression: 1.6% generalized anxiety disorder: 2.4%
Weiss 2005 International	RCT, DB parallel	Children aged 8-12 years with ADHD (any subtype as defined by DSM-IV were eligible. Symptom severity had to be >1.0 standard deviation (SD) above age and sex norms on the ADHD Rating Scale -IV-Teacher Version: Investigator administered and scored (ADHDRS-IV-Teacher:Inv). Patients were also required to have a mean Conners Parent Rating Scale (CPRS-R:S) ADHD index score at least 1.5 SD above age and sex norms.	ODD: 33.3% Generalized anxiety disorder: 2.6% Learning disorder: 29.8% Motor skills disorder: 6.5% Communications disorder: 8.1%

Dexmethylphenidate XR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Michelson 2004	atomoxetine 1.2mg/kg/day-1.8mg/kg/day for the first 10 weeks then atomoxetine or placebo for 9 months Duration: 9 months	NR	NR	ADHD RS and Clinical Global Impressions of Severity (CGI-S): primary assessments, bi-weekly. Child Health Questionnaire, Children's Depression Rating Scale, Conners Parent Rating Scale-Revised: Short, Conners Teacher Rating Scale-Revised: Short, WISC-III, and the Multidimensional Anxiety Scale.
Weiss 2005 International	Atomoxetine 1.2 to 1.8 mg/kg/d (n=101) Placebo (n=52) 2:1 7-weeks' treatment Mean dose: 1.33 mg/kg of atomoxetine	NR / 5 days	No	Primary efficacy measure: ADHDRS-IV-Teacher:Inv; interviews with primary classroom teacher within 4 days before each clinical visit. Secondary measures: Conners Global Index-Teacher; the Social Skills Rating System-Teacher (SSRS-T); the Brown Attention-Deficit Disorder Scales: Teacher version; the Academic Performance Rating Scale; the Behavioral Grade Measure, CGI-I and CGI-S; and the Conners Parent Rating Scale (CGI-I and CGI-S completed at each visit by investigator; parents completed Conners Parent Rating scale at each visit). All measures were tested at baseline and endpoint.

Dexmethylphenidate XR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Michelson 2004	Atomoxetine: n=292 Mean age: 10.6 years 89.4% male Ethnicity: NR Placebo: n=124 Mean age: 10.1 years 90.3% male Ethnicity: NR	Atomoxetine: n=292 ADHD subtype combined: 72.6% hyperactivity/implusive: 4.5% Inattentive: 22.9% Previous stimulant treatment: 53.8% Placebo: n=124 ADHD subtype combined: 74.2% hyperactivity/implusive: 4.8% Inattentive: 21.0% Previous stimulant treatment: 50.0%	NR/NR/604	10/NR/414
Weiss 2005 International	Mean age: 9.9 years 80.4% male Ethnicity: NR	Mean baseline CGI-S score: 4.9 (SD=0.8)	241 / 153 / 153	21 / 3 / 132

Dexmethylphenidate XR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Michelson 2004	Survival curve, proportion not relapsing: atomoxetine>placebo, p<0.001 Atomoxetine baseline: change from baseline vs. placebo baseline: change from baseline *ADHD RS* - 15.8: 6.8 vs 15.7: 12.3, p<0.001 *CGI-S score* - 2.3: 0.9 vs 2.2: 1.4, p=0.003 *CPRS* - oppositional, 6.5: 1.6 vs 5.4: 2.7, p=0.027; cognitive problems, 7.3: 1.9 vs 6.8: 3.7, p<0.001; hyperactivity- 4.5: 1.5 vs 4.6: 3.1, p=0.001; ADHD index, 13.7: 3.7 vs 13.3: 6.9, p<0.001 *CTRS* - all NS *CHQ* - 43.4: -5.6 vs 44.0: -9.5, p=0.016	Self-report
Weiss 2005 International	Atomoxetine vs placebo: Responders, defined as a 20% reduction in ADHDRS-IV-Teacher:Inv : 69% vs 43.1%, p=0.003 Responders, defined as endpoint ADHDRS-IV_Teacher:Inv scire within 1 SD of the mean for age and sex: 68% vs 51%, p=0.51 Change in scores from baseline: ADHDRS-IV-Teacher:Inv, Total: -14.5 vs -7.2, p=0.001 Inattentive subscale: -7.5 vs -4.3, p=0.16 Hyperactive/impulsive subscale: -7.0 vs -3.0, p<0.001 CGI-S: -1.5 vs -0.7, p=0.001 CGI-I: +2.6 vs +3.4, p<0.001 Conners Global Index-Teacher: -3.7 vs -0.8, p=0.008 Brown ADD Scale:Teacher: Combined T score: -5.0 vs -2.9, p=0.072 Effort T score: -4.6 vs -1.9, p=0.046 Action T score: -5.7 vs -2.9, p=0.052 APRS, total: +4.8 vs +2.2, p=0.106 Social Skills Rating-Teacher: Problem behavior: -5.3 vs -2.0, p=0.025 Social skills: +4.0 vs +2.4, p=0.196 Conners Parent Rating Scale-Revised Oppositional scubscale: -5.4 vs -1.6, p=0.276 Cognitive Problems subscale: -11.8 vs -3.8, p<0.001 Hyperactivity subscale: -12.2 vs -4.2, p<0.001 ADHD Index: -12.1 vs -4.1, p<0.001	Assessed by open-ended discussion at each clinic visit

Dexmethylphenidate XR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Michelson 2004	atomoxetine: placebo number of adverse events- 191(65.6%): 66(53.7%), p=0.027 mean weight gain- 1.2: 3.3, p<0.001 mean height gain- 2.5: 2.9, p=0.088 NS in routine chemistry, liver function tests, hematological measures, or cardiac QT intervals(corrected for heart rate)	atomoxetine: 9(3.1%) placebo: 1(0.8%) p=0.293	
Weiss 2005 International	Atomoxetine vs placebo: Decreased appetite: 24.0% vs 3.8%, p=0.001 Somnolence: 17.0% vs 3.8%, p=0.020 Change in weight: -0.67 vs +1.21, p<0.001 Change in heart rate: +3.3 bpm vs -0.1 bpm, p=0.67 Vomiting: differences were not statistically significant Discontinuations (n=6) due to AEs in Atomoxetine group were due to: abdominal pain (n=2), emotional disturbance (n=1), feeling abnormal (n=1), irritability (n=1), vomiting (n=1)	21 ; 6 (all in atomoxetine group) 83.2% of atomoxetine patients completed the study (84 of 101) 92.3% of placebo patients complete study (48 of 52)	

Dexmethylphenidate XR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Silva 2006	RCT DB crossover	Boys and girls 6–12 years of age who had been diagnosed with ADHD were eligible for enrollment. Patients eligible for inclusion were required to fulfill the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for ADHD of any type, as established by the Computerized Diagnostic Interview Schedule for Children (C-DISC-4). Patients must also have been stabilized on 20–40 mg/day of MPH for at least 1 month prior to screening. Only those patients whose parents and/or guardians provided written, informed consent were enrolled. Assent was also obtained from all children (documented by signature of those older than 9 years). Girls were required to be premenarchal, sexually abstinent, or using a reliable contraceptive method. Sexually active girls were required to show negative results on a urine pregnancy test. At screening (days –14 to –7), all prospective patients underwent a physical examination, an electrocardiogram (ECG), blood and urine sampling for routine laboratory tests, urine drug screening, and, for girls, a urine pregnancy test. Informed consent was also documented. A complete medical and psychiatric history was obtained, and the C-DISC-4 was conducted to confirm ADHD diagnosis. Children were excluded if the investigator deemed the child's IQ was below average or if there was evidence of an IQ below 80, or if they were home schooled, were diagnosed with Tourette syndrome or a tic disorder, had a concurrent or history of a significant medical or psychiatric illness (schizophrenia, bipolar disorder, or autism) or substance abuse disorder, or if they or their parents or guardians were unable to understand or follow instructions necessary to participate in the study. Patients taking antidepressants, those who had initiated psychotherapy within 3 months preceding screening, and those with a positive urine drug screen, were also ineligible. Children with poor response or intolerance to MPH, currently taking other medications for ADHD, taking or planning to take another investigational drug within 30 days of study start, or who had previously participated in d-MPH-ER studies were also excluded.	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Silva 2006	d-MPH-ER 20 mg/day or placebo	NR/NR	NR/NR	Primary Outcome Measure: the Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale (SKAMP)-Combined scores Other Measures: SKAMP Deportment and Attention subscales, Math—Attempted, and Math—Correct scores

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Silva 2006	Mean age= 9.4 yrs (SD 1.6) (Range: 6-12 yrs) 70.4% male Ethnicity NR ("predominantly Caucasian")	**DSM-IV ADHD diagnosis N(%)** Inattentive: 5 (9.3) Hyperactive/impulsive: 0 Combined Type: 49 (90.7) **ADHD mean duration, years (SD**): 4.6 (1.6)	54/NR/54	1/0/53

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Silva 2006	modafinil vs. placebo SKAMP-Combined scores adjusted mean: -10.014 vs. 0.878, p<0.001 SKAMP Deportment scores, mean change at 12 h postdose: -0.3 vs. 3.6, p=0.001 -estimated from graphic SKAMP Attention score, mean change at 12 postdose: 1.7 vs. 2.6, p=0.046 -estimated from graphic Math—Attempte, mean change at 12 postdose: 20 vs. -11, p< 0.001 -estimated from graphic Math—Correct scores, mean change at 12 postdose: 18 vs. -10, p< 0.001 -estimated from graphic	spontaneaous reporting by subjects and parents

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Silva 2006	dcreased appetite anorexia: 9.4% vs. 0% fatigue: 3.85% vs. 0% insomnia: 3.85% vs. 0% headache: 1.9% vs. 5.6% irritability: 0% vs. 5.6%	1-Jan	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Greenhill 2006	RCT DB	Eligible participants were males and females 6 to 17 years of age who met DSM-IV criteria for ADHD of any type, as established by a psychiatric examination and a semistructured diagnostic interview (the ADHD module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version). For boys, baseline scores on the Conners ADHD/DSMIV Scale-Teacher version (CADS-T) DSM-IV total subscale were required to be ≥27 for those 6 to 8 years old, ≥24 for those 9 to 11 years old, ≥19 for those 12 to 14 years old, and ≥14 for those 15 to 17 years old. For girls, the respective baseline cutoff scores on the CADS-T were ≥16, ≥13, ≥12, and ≥6. All of the patients were attending school in a classroom setting and had the same teacher for the duration of the study who was able and willing to perform symptom assessments. Patients had to be functioning at age-appropriate levels academically, and female patients who had reached menarche were required to have a negative pregnancy test and to be using adequate and reliable contraception throughout the study. Excluded were those patients with clinically significant abnormalities in vital signs, physical examinations, or laboratory tests; those with a history of seizures or use of anticonvulsant medication, comorbid psychiatric conditions (obtained by clinical interview); those with any medical condition that could interfere with study participation or assessments or that may pose a danger with administration of methylphenidate; those taking psychotropic medications; and those who initiated psychotherapy within the past 3 months. Patients with a positive urine drug screen or with a history of poor response or intolerance to methylphenidate were also excluded, as were those who were pregnant or nursing or were taking any other investigational drug within 30 days of study entry.	None
Lisdexamphetamine			
Biederman 2007	RCT DB	Male and female children aged 6 to 12 years who met DSM-IV criteria for ADHD and ADHD-RS-IV score >= 28	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Greenhill 2006	d-MPH-ER: Mean Final Dose = 24.0 mg/day (SD 7.1) ; Dose Range: 5-30 mg/day Placebo: Mean Final Dose: 26.9 mg/day (SD 7.1)	5-week dose titration phase/NR	NR/NR	Primary Outcome Measure: Conners ADHD/DSM-IV Scale - Teacher version (CADS-T) total subscale score Other Measures: CADS-T Inattentive and Hyperactive-Impulsive subscale scores, CADS-P DSM-IV total subscale score and Inattentive and Hyperactive-Impulsive subscale scores, Clinical Global Impressions-Improvement (CGI-I) and CGI-Severity (CGI-S) scale scores, and Child Health Questionnaire Parent Form 50 scores
Lisdexamphetamine				
Biederman 2007	LDX 30, 50, or 70 mg with forced-dose titration, or placebo 1 week screening 1 week wash out and 4 weeks treatment 30 mg for 4 weeks, 50 mg (30 mg/d for week 1, with forced-dose escalation to 50 mg/d for weeks 2-4), or 70 mg (30 mg/d for week 1, with forced-dose escalation to 50 mg/d for week 2 and 70 mg/d for weeks 3 and 4), or placebo all 4 weeks	1 week wash out	None	Weekly assessments of ADHD-RS Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) CGI-I

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Greenhill 2006	Mean age= 10 yrs (Range: 6-17 yrs) 64% male 60.1% white	D-MPH-ER vs. Placebo, NS between groups **DSM-IV ADHD diagnosis N(%)** Inattentive: 22 (21.4) Hyperactive/impulsive: 2 (1.9) Combined Type: 79 (76.7) **Duration of ADHD symptoms, yr** Mean (SD): 5.3 **Received Medication for ADHD in the past N(%)** Yes: 40 (38.8) No: 63 (61.2) **Baseline CADS-T total subscale score** Mean: 34.3 **Baseline CADS-P total subscale score** Mean: 39.5 **Baseline CGI-S rating N(%)** 4: 65 (63.1) 5: 35 (34.0) 6: 3 (2.9)	NR/NR/103	NR/NR/97
Lisdexamphetamine				
Biederman 2007	Mean age: 9 yrs. 69% male 53% white		NR/NR/297/290 randomized	60 withdrawals/ 11 / 285 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Greenhill 2006	**d-MPH-ER vs. Placebo** Conners ADHD/DSM-IV Scale - Teacher version (CADS-T) total subscale score: 16.3 vs. 5.7, p<0.001 CADS-T Inattentive: 8.1 vs. 3.3, p=0.001 CADS-T Hyperactive-Impulsive: 8.2 vs. 2.5, p<0.001 CADS-P DSM-IV total subscale score: 17.6 vs. 6.5, p<0.001 CADS-P Inattentive: 9.5 vs. 3.2, p<0.001 CADS-P Hyperactive-Impulsive: 8.2 vs. 3.3, p<0.001 CGI-I, very much improved or much improved at final visit: 67.3% vs. 13.3%, p<0.001 CGI-S at final visit: moderately ill: 32.0% vs. 64.0% markedly ill: 4% vs. 21.4% severly ill: 0% vs. 2.4% CHQ physical component: NS CHQ psychological component:11.9 vs. 4.3, p<0.001	spontaneously reported
Lisdexamphetamine		
Biederman 2007	At 4 weeks of treatment ADHD-RS-IV total score) was significantly greater with each of the 3 LDX doses compared with placebo (P < 0.001, d[= 3256, F = 35.16) (Data in graphs) Effect sizes based on the ADHD-RS-IV were LDX30 1.21, LDX50 1.34, and LDX70 1.60 (by the corresponding between-group differences and the model-based SD of 12.84). CPRS-R scores were significantly better in active groups than Placebo throughout study (P< 0.01, Data=NR) CGI-I ratings were either "very much improved" or "much improved" in _>70% of patients in the active-treatment groups, compared with 18% of patients receiving placebo. (Data= NR)	Observation and asking a non-leading question

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Greenhill 2006	D-MPH-ER vs. placebo (%) Total Adverse Events: 75.5 vs. 57.4, NS Decreased appetite: 30.2 vs. 8.5, p=0.0068 Headache: 24.5 vs. 10.6, NS Abdominal Pain, Upper: 13.2 vs. 12.8, NS Nausea: 11.3 vs. 6.4, NS Nasopharyngitis: 9.4 vs. 6.4, NS Upper respiratory tract infection: 9.4 vs. 6.4, NS Dyspepsia: 7.5 vs. 4.3, NS Insomnia: 7.5 vs. 6.4, NS Abdominal Pain: 5.7 vs. 0, NS Initial Insomnia: 5.7 vs. 4.3, NS Affect lability: 3.8 vs. 0, NS Anorexia: 3.8 vs. 2.1, NS Diarrhea: 3.8 vs. 2.1, NS Fatigue: 3.8 vs. 4.3, NS Gastroenteritis: 3.8 vs. 0, NS Influenza: 3.8 vs. 8.5, NS Irritability: 3.8 vs. 2.1, NS Otitis media: 3.8 vs. 2.1, NS Stomach Discomfort: 3.8 vs. 0, NS Vomiting: 3.8 vs. 4.3, NS	19/1	
Lisdexamphetamine			
Biederman 2007	Treatment Emergant Aes (%) Any Events **LDX30 71.8 LDX50 67.6 LDX70 83.6** Placebo 47.2 Decreased appetite **LDX30 36.6 LDX50 31.1 LDX70 49.3** Placebo 4.2 Insomnia LDX30 15.5 LDX50 16.2 LDX70 24.7 Placebo 2.8 Irritability **LDX30 11.3 LDX50 8.1 LDX70 9.6** Placebo 0 Dizziness **LDX30 7.0** LDX50 5.4 LDX70 2.7 Placebo 0 Vomiting LDX30 7.0 LDX50 5.4 **LDX70 13.7** Placebo 4.2 Weight loss LDX30 5.6 LDX50 2.7 **LDX70 19.2** Placebo 1.4 Dry mouth LDX30 2.8 LDX50 2.7 **LDX70 8.2** Placebo 0 **P=< 0.05 compared to placebo**	LDX30 15 LDX50 14 LDX70 13 Placebo 18; LDX30 4 LDX50 4 LDX70 10 Placebo 1	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Biederman 2007	RCT DB crossover	6 to 12 years Combined or predominantly hyperactive-impulsive ADHD according to DSM-IV Stable regimen of stimulants at least 1 month out of previous 6 months Adequate response to stimulants based on clinical assessment Functioning at age appropiate academic level	None
Methamphetamine			
Hall 1973	RCT DB	Male outpatients; with pre-drug age 72-132 months; normal IQ (WISC 80 or above); personality and adjustment difficulties as indicated by one or more combinations of the following behaviors: excitable, impulsive, poor judgment, learning achievement not commensurate with measures of general intelligence, restless or immature, low frustration tolerance, distractability, shor attention span emotional lability, mood changes quicly, clumsy, poor motor cordination; free of observable psychotic behaviors; general diagnostic category due to minimal brain dysfunction; no medical illness which contrindicated stimulant therapy; no concurrent medication during the study; no sever seizures or significant sensory and/or gross motor deficits; any previous stimulant therapy must be discontinued.	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Biederman 2007	Dose-titration phase: open administration of MAS XR (10, 20 or 30) to determine "optimal" dose Double-blind crossover period: 1 week each of MAS XR, corrsponding doses of LDX (30, 50, 70) and placebo	Run in of 3 weeks Adderall titration	NR	Least squares mean of average scores of: SKAMP-DS CGI Permanent Product Measure of Performance-Attempted (PERMP-A)
Methamphetamine				
Hall 1973	Desoxyephedrine (time released formula) 5 mg/day taken in morning for first 2 weeks Dose increase to 10 mg/day for following 2 weeks (one child required 15mg dose)	NR/NR	NR	Wechsler Intelligence Scale for Children (WISC, 1955) on either pre- or on-drug, Matching Familiar Figures Test (MFFT)Porteus Maze Test (PM), Paired Associate Learning Test (PALT), Werry-Weiss-Peters Activity Scale (WW)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Biederman 2007	Mean age: 9.1 years 63% male 56% white	Combined type: 100% Mean age of ADHD onset: 5.8 yrs Mean time since diagnosis: 3.3 yrs Prior treatment Amphetamine: 44.2% MPH: 26.9% Stimulant NOS: 11.5% Stimulants with atomoxetine: 9.6% CGI severity Moderately ill: 61.5% Markedly ill: 21.2% Severity ill: 17.3%	NR/52/52	2/1/50
Methamphetamine				
Hall 1973	Mean age: 6.9 yrs. 100% male 93% white	**Class placement, N (%)** regular: 21 (65.6) educationally handicapped: 4 (12.5) limited day: 3 (9.4) aphasia: 2 (6.3) home teacher: 2 (6.3) previously medicated, N (%) Yes: 8 (25) No: 24 (75)	40/32/32	NR/NR/32

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Biederman 2007	LDX vs MAS XR vs placebo; p<0.0001 for all comparisons of each drug to placebo, respectively SKAMP-DSL 0.8 vs 0.8 vs 1.7 PERMP LS mean: 133.3 vs 133.6 vs 88.2 CGI-I: LS mean: 2.2 vs 2.3 vs 4.2 % much improved: 42% vs 56% vs 18% % very much improved: 32% vs 16% vs 18%	NR
Methamphetamine		
Hall 1973	**desoxyephedrine vs. placebo, mean change** **PALT** Trials: 0.37 vs 1.82 Errors: -1.94 vs. 11.13 **MFFT** Latency: 2.47 vs. -1.50 Errors: -6.75 vs. -0.87 **PM** TA: 1.25 vs. 0.60 TQ: 8.19 vs. 4.75 **Digit Span:** 0.44 vs. 0.76 **WISC** Verbal IQ: 7.17 vs. -0.75 Perf. IQ: 10.31 vs 5.25 FS IQ: 8.19 vs. 2.43 **WW:** -8.62 vs. -1.25	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Biederman 2007	LDX vs MAS XR vs placebo Any: 8 (16%) vs 9 (18%) vs 8 (15%) Upper abdominal pain: 0 vs 2 (4%) vs 1 (2%) Upper respiratory tract infection: 1 (2%) vs 1 (2%) vs 0 Decreased appetite: 3 (6%) vs 2 (4%) vs 0 Insomnia: 4 (8%) vs 1 (2%) vs 1 (2%) Vomiting: 0 vs 1 (2%) vs 2 (4%) Anorexia: 2 (4%) vs 0 vs 0	Total withdrawals: 0 vs 0 vs 2 Withdrawals due to adverse events: 0 vs 0 vs 1	
Methamphetamine			
Hall 1973	NR	NR/NR	dissertation

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
MPH ER (Metadate®)			
Greenhill 2002	RCT, DB (randomized 1:1 to MPH MR vs. placebo)	Children 6-16 years old with a primary diagnosis (based on parent interview using the NIMH Diagnostic Interview Schedule for Children - version 4.0) of AHDH, combined subtype or the predominately hyperactive-impulsive subtype as defined in DSM-IV (diagnostic code 314.01), who were in first grade or higher with a single teacher who could assess their behavior in the morning and afternoon on specified days. Exclusion criteria: comorbid psychiatric diagnosis; history of seizure, tic disorder, or family history of Tourette's syndrome; female having undergone menarche; use of amphetamines, pemoline, or an investigational drug within 30 days of study entry; concomitant use of clonidine, anticonvulsant drugs, or medications known to affect blood pressure, heart rate, or central nervous system function; hyperthyroidism or glaucoma; any concurrent chronic or acute illness (eg, allergic rhinits, severe cold) or disability that could confound the study results. Also excluded were children who had failed a previous trial of stimulants for ADHD, had required a third daily dose in the afternoon or evening, had a documented allergy or intolerance to MPH, or were living with anyone who currently had substance abuse disorder (excluding dependency).	None reported
MPH transdermal patch			

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
MPH ER (Metadate®)				
Greenhill 2002	3-week treatment period. Doses taken at breakfast. Doses began at 20 mg/day and were to be individually titrated up to be: Week 1: 20 mg/day of MPH MR or 20 mg/day for placebo Week 2: 40 mg/day of MPH MR or 36.8 mg/day for placebo Week 3: 60 mg/day of MPH MR or 51.6 mg/day for placebo Mean total daily dose (MPH MR) for week 1: 20 mg/d (0.64 mg/kg/day); mean total daily dose (MPH MR) for week 2: 32.3 mg/d (1.02 mg/kg/day); mean total daily dose (MPH MR) for week 3: 40.7 mg/d (1.28 mg/kg/day). By week 3, 25% (n=38) were taking 20 mg/day of MPH MR; 38% (n=59) were taking 40mg/day; and 28% (n=43) were taking 60 mg/day.	1-week, single-blind run-in period with placebo. 45 (n=24%) of children screened were found to be placebo-responders and were disqualified.	No	Primary efficacy measure: Conners' Teachers Global Index (10 items), completed by phone interview in the morning (~10am) and afternoon (~2 pm) of three alternating days of each treatment week. Secondary efficacy measures: Conners' Parent Global Index (10 item) completed on 1 day of each weekend during the morning, afternoon, and evening. Parents were also asked to complete a global assessment at the final visit, using a diary of observations they had kept during the run-in placebo week.
MPH transdermal patch				

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
MPH ER (Metadate®)				
Greenhill 2002	Mean age =9 years Male=81.8% White = 81.4% African American = 15.3% Hispanic = 10.2% Other = 3.5%	Previously treated for ADHD = 64 .0%(n=201) Mean Conners' Global Index - Teacher = 12.1 Mean Conners' Global Index - Parent = 13.2 Mean CGI Severity of Disorder = 4.45	507 screened/ 321 eligible /321 enrolled	45 withdrawn (n=28 from placebo, n=17 from MPH MR) /NR /314 analyzed (n=155 MPH MR; n=159 placebo)
MPH transdermal patch				

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
MPH ER (Metadate®)		
Greenhill 2002	At endpoint, investigators rated 64% of children as moderately or markedly improved with MPH MR treatment, compared with 27% of the placebo group. Conners' Global Index - Teacher's Scores (MPH MR vs. placebo): Baseline mean (Standard deviation): 12.7 (7.2) vs. 11.5 (7.35) (p=0.1309) Week 1 mean (SD): 7.3 (4.93) vs. 10.9 (6.56) (p=0.0001) Week 2 mean (SD): 5.8 (4.71) vs. 10.4 (6.75) (p=0.0001) Week 3 mean (SD): 4.7 (4.77) vs. 9.2 (6.30) (p=0.0001) Least suqares mean changes between treatment groups differed significantly in favor of MPH MR group (95% CI: 5.26-8.09, t=9.27, df=311, p<0.001). Effect size (calculated from teacher assessment) = 0.78 for MPH MR vs. placebo during last week of treatment. Conners' global index - Teacher's scores (MPH MR vs. placebo) Baseline mean (Standard deviation): 13.6 (6.6) vs. 12.9 (7.6) (p=NR) Weeks 1 and 2: data not specified Week 3 mean (SD): 7.4 (5.9) vs. 10.1 (6.7) (p=NR) Least squares mean change between treatment groups differed significantly in favor of MPH MR group (95% CI: 1.7-4.9, t=3.97, df=297, p<0.001). Effect size (calculated from parent assessment) = 0.4 for MPH MR vs. placebo during last week of treatment.	Reported and observed AE's. Vital signs were collected at baseline and weekely therafter. Parents completed the Pittsburgh 11-item side effect questionnaire the same day they completed the Conners'Global Index. Teachers also filled out a similar side effect questionnaire 3 times per week near the end of the school day, on the same days they filled out the Conners' Global Index.
MPH transdermal patch		

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
MPH ER (Metadate®)			
Greenhill 2002	Any Adverse Event (AE) reported: 51.6%(n=80) in MPH MR; 37.9% (n=61) in placebo Headache: 14.8% (n=23) in MPH MR; 10.6% (n=17) in placebo Anorexia: 9.7% (n=15) in MPH MR; 2.5% (n=4) in placebo [anorexia more significant in MPH MR group than in placebo; p=0.007] Abdominal Pain: 9.7% (N=15) in MPH MR; 5.0% (n=8) in placebo Insomnia: 7.1 %(n=11) in MPH MR: 2.5% (n=4) in placebo (these AE's are spontaneous AE's occuring at an indcidence >=5% in either treatment group) AE's determined by investigator to be related to study medicine: 32.9% of MPH MR and 17.4% of placebo (Of the two withdrawals due to AE's, one child developed a pruritic, nonerythematous, periumbilical rash on the 6th day of MPH MR treatment; whereas the other childre developed a headache on Day 4 and dizziness + stomachache on Day 5 of MPH MR treatment.)	45 withdrawals; 2 withdrawals due to adverse events	
MPH transdermal patch			

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
McGough 2006	RCT DB crossover	Eligible participants were children between the ages of 6 and 12 years, inclusive, diagnosed with ADHD by Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria. Diagnosis of ADHD and screening for co-occurring psychopathology was based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (KSADS-PL) and comprehensive clinical psychiatric interviews. The Kaufman Brief Intelligence Test (KBIT) was used to assess mental capacity. Participants were not permitted to enroll if they had a comorbid psychiatric diagnosis (with the exception of oppositional defiant disorder), a history of seizures or tic disorders, mental retardation, or any illness or skin disorder that might jeopardize safety or compromise study assessments. Participants were required to have a total score of ≥26 on the ADHD Rating Scale–Fourth Edition at baseline (unmedicated), normal laboratory parameters and vital signs including electrocardiogram (ECG) results, and could not have taken clonidine, atomoxetine, antidepressants, investigational medications, hepatic, P450 enzyme altering agents, medications with central nervous system effects, sedatives, anxiolytics, or antipsychotics within the 30 days prior to screening. Participants were either known to be responsive to stimulants or naïve to stimulant treatment.	patients with concurrent ODD allowed, proportion of ODD patients not reported

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
McGough 2006	Methylphenidate: Total daily doses of 10, 16, 20, or 27 mg, delivered over the 9-hour patch wear time Mean Dose: NR	lead-in open label dose optimiation phase/NR	NR/NR	Primary Outcome Measure: the Deportment subscale of the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Teacher Rating Scale measured at multiple time points (predose and 2, 3, 4.5, 6, 7.5, 9, 10.5, and 12 hours postdose) Other Measures: Permanent Product Measure of Performance (PERMP) Derived Measures, the ADHD Rating Scale IV completed by investigators after parental interviews, and the Conners' Parent Rating Scale–Revised Short Version (CPRS-R), Clinical Global Impressions (CGI-S and CGI-I) and Parent Global Assessment (PGA)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
McGough 2006	Mean age= 9.1 yrs (SD .7) 72% male 70% white	**ADHD subtypes n (%)** Inattentive: 13 (17) Hyperactive/Impulsive: 4 (5) combined: 62 (79) **ADHD Rating Scale, Mean (SD):** 41.8 (7.6) **CGI-S, Mean (SD)**: 4.4 (0.7)	NR/NR/93	13/2/79

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
McGough 2006	**Teacher Rating Treatment/Period/Sequence/Subject-within-sequence,** SKAMP-D, F(1.77): 71.48(p<.0001)/1.25(p=.2664)/.79(p=.3767)/3.26(p<.0001) SKAMP-A, F(1.77): 83.04(p<.0001)/.97(p=.3266)/1.56(p=.2156)/4.98(p<.0001) PERMP-number attempted, F(1.77): 46.34(p<.0001)/3.81(p=0544)/1.42(p=2365)/8.98(p<.0001) PERMP-number correct, F(77.77): 56.24(p<.0001)/6.15(p=.0153)/1.33(p=.2520)/9.97(p<.0001) **Other Measures, MTS vs. placebo** LS Mean SKAMP-D (+/-SE): 3.2 (0.58) vs. 8.0 (0.58), p<0.0001 LS Mean SKAMP-A (+/-SE): 6.2 (0.50) vs. 9.9 (0.50), p<0.0001 ADHD Rating Scale IV: 16 vs. 32, p<0.0001 [estimated from graphic] CPRS-R: 19 vs. 35, p<0.0001 [estimated from graphic] CGI-I: 79.8% vs. 11.6%, p<0.0001 Parent Global Assessment: 71.1% vs. 15.8%, p<0.0001	open-ended investigator inquiry at onset, every visit and study ending

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
McGough 2006	**MPH vs. placebo, n (%)**	13/7	
	Any adverse event: 24 (30.0) vs. 18 (22.5) Headache: 3(3.8) vs. 3(3.8) Anorexia: 2(2.5) vs. 0 Pharyngolaryngeal Pain: 2(2.5) vs. 1(1.3) Rash: 1(1.3) vs. 2(2.5) Nasopharnyngitis: 1(1.3) vs. 2(2.5) Nausea: 3(3.8) vs. 0 Rhinitis allergic: 2(2.5) vs. 0 Blood Pressure Increased: 2(2.5) vs. 0 Lymphadenopathy: 2(2.5) vs. 0 Upper Respiratory Tract Infection: 0 vs. 3(3.8)		

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Modafanil			
Rugino 2003 Fair	RCT, DB, Parallel groups Setting: Regional development center	(1) reliable transportation to and from the development center; (2) regular school attendance; (3) an average Conners Teacher Rating Scale ADHD index t score of 70 or higher; (4) an average percentile score for the ADHD Rating Scale IQ of 70 or higher; and (5) a verbal intelligence quotient of 80 or higher.	ODD/Conduct=6 (27.3%) Separation anxiety=13.6% Specific phobia=18.2% Enuresis=13.6% Learning disorder=18.2% Borderline intelligence quotient=9.1% Adjustment disorder=9.1% Selective mutism=4.5%

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Modafanil				
Rugino 2003 Fair	Modafinil mean dose=264 mg Placebo Flexible dosing Dosing schedule=once each morning Mean study duration=5.6 weeks	NR/NR	NR	Test of Variables of Attention (TOVA) ADHD Rating Scale IV Conners' Parents Ratings Scales Revised-L (CPRS) Conners' Teachers Rating Scales Revised-L (CTRS)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Modafanil				
Rugino 2003 Fair	Mean age=7.9 62.5% male 100% white	ADHD type Combined=72.7% Inattentive=18.2% Hyperactive-impulsive=4.5%	NR/NR/24	2 (8.3%) withdrawn/0 lost to fu/analyzed=22 (modafinil=11, placebo=11)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Modafanil		
Rugino 2003 Fair	Modafinil vs placebo (t scores representing post-treatment improvement) DSM-IV symptoms (CTRS and CPRS): 68.2 vs 76, p<0.05 Other Conners ADHD Scales (% of 14 scales with mean t score difference more negative than -5): 13 (92.8%) vs 1 (7.1%), p<0.001 ADHD Rating Scale raw scores: 14 vs 14.7, p=NS % parents rating "significant" overall improvement: 10 (90.9%) vs 8 (72.7%), p<0.004	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Modafanil			
Rugino 2003 Fair	Delayed sleep onset: 4 (36.4%) vs 4 (36.4%) Modafinil (n=11) Transient stomachache=2 (18.2%) Occasional transient headache=1 (9.1%) Transient mood disorder with tearfulness=1 (9.1%) Placebo (n=11) Sleepiness=1 (9.1%) Irritability=1 (9.1%) Decreased appetite=1 (9.1%) Tonsillitis/pharyngitis=1 (9.1%)	Total withdrawals: 2/13 (15.4%) vs 0 Withdrawals due to adverse events: nr	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Greenhill 2006	RCT DB	Eligible patients met the following inclusion criteria: 6 to 17 years of age, inclusive; the National Institute of Mental Health Diagnostic Interview Schedule for Children, Fourth Edition (DISC-IV) was used to establish the patients' diagnosis of ADHD using the full DSM-IV diagnostic criteria; Clinical Global Impression of Severity of Illness (CGI-S) rating of 4 or higher (moderately ill or worse); weight and height between the 5th and 95th percentile based on the National Center for Health Statistics; intelligence quotient of at least 80; absence of learning disabilities, with a score of at least 80 on the Wechsler Individual Achievement Test, Second Edition, Abbreviated; attending a full-time school (not home school), with a teacher and parent or legal guardian willing to participate; and total and/or factor scores on the teacher-/investigator-rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version at least 1.5 standard deviations (SD) above the norm for the patient's age and gender. Patients were excluded if they had a history or current diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders (DSM-IV axis I); any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk; or ADHD symptoms well controlled on current therapy with tolerable side effects. Patients who had failed to respond to two or more adequate courses (dose and duration) of stimulant therapy for ADHD were also excluded. Additional exclusion criteria were absolute neutrophil count (ANC) below 1 X 109/L; hypertension (defined as systolic blood pressure [SBP] ≥122 mmHg or diastolic blood pressure [DBP] ≥78 mmHg for children 6 to 9 years old; ≥126 mmHg or ≥82 mmHg, respectively, for ages 10 to 12; and ≥136 mmHg or ≥86 mmHg, respectively, for ages 13 to 17); hypotension (defined as sitting SBP <50 mmHg for children <12 years of age, <80 mmHg for children ≥12 years of age); resting heart rate outside the range of 60 to 115 beats per minute; a history of alcohol or substance abuse as defined by DSM-IV criteria; and consumption of >250 mg/day of caffeine. Concomitant use of prescription or nonprescription agents with psychotropic properties, including ADHD treatments and dietary supplements, was prohibited within 1 week of the baseline visit and during the study. Monoamine oxidase inhibitors and selective serotonin reuptake inhibitors were prohibited within 2 weeks of baseline testing and throughout the study.	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Greenhill 2006	Modafinil: Mean Dose: 361.4 mg (SD 90.9) Dose Range: 85 to 425mg Placebo: Mean Dose: 383.1 mg (SD 85.5) Dose Range: 85 to 425mg	washout 7d before baseline testing	none/NR	Primary Outcome Measure: total score on the teacher-/investigator-rated ADHD-RS-IV School Version Other Measures: the ADHD-RS-IV Home Version, Clinical Global Impression of Improvement (CGI-I), factor scores derived from the Test of Variables of Attention (TOVA), factor scores for inattention and hyperactivity derived from the Conners' Parent Rating Scale-Revised, Short Form (CPRS:R-S), factor scores from the Social Skills Rating Scale (SSRS), and Child Health Questionnaire (CHQ)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Greenhill 2006	Mean age= 9.9 yrs (Range: 6 - 16 yrs) 73% male 72% white	Modafinil vs. Placebo **CGI-S Score, N(%)** Moderately ill: 76 (38) Markedly ill: 87 (44) Severely ill: 34 (17) Not Assessed: 1 (0.5) **Current ADHD Subtype, N(%)** Inattentive: 47 (24) Hyperactive/impulsive: 10 (5) Combined: 139 (70) **Previous ADHD Treatement, N(%):** 109 (55) MPH: 73 (37) Amph. Salts: 64 (32) ATX: 27 (14) Other: 22 (11) **Most Frequently Coadministrered Agents N(%)** Nonopioid anakgesics/anti-inflammatories: 65 (33) Respiratory agents: 33 (17) Antihistamines: 28 (14) Anti-infectives: 24 (12) **ADHD-RS-IV total score, mean** School Version: 38.5 Home Version: 40.8	295/NR/200	59/5/194

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Greenhill 2006	Modafinil vs. placebo , mean change **ADHD-RS-IV School version** Total score: -17.5 vs.-9.8, p<.0001 Inattention: -9.7 vs. -4.9, p<.0001 Hyperactivity/impulsivity: -7.9 vs. -4.8, p=.003 **ADHD-RS-IV Home version** Total score: -17.6 vs. -7.7, p<.0001 Inattention: -9.2 vs. -3.5, p<.0001 Hyperactivity/impulsivity: -8.3 vs. -4.2, p=.0001 TOVA **ADHD score**: -0.4 vs. 1.1, p=.001 **CPRS:R-S** **ADHD index**: -12.7 vs. -6.3, p=.001	general inquiry and spontaneous reporting

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Greenhill 2006	Modafinil vs. Placebo, N(%) Insomnia : 37(28) vs. 5(7), p<.05 Headache : 29(22) vs. 6(9), p<.05 Decreased appetite: 23(18) vs. 2(3), p<.05 Abdominal pain: 16(12) vs. 3(4), NS Infection: 14(11) vs. 6(9), NS Increased cough: 12(9) vs. 6(9), NS Pharyngitis: 11(8) vs. 9(13), NS Rhinitis: 10(8) vs. 7(10), NS Vomiting: 8(6) vs. 4(6), NS Emotional Lability: 7(5) vs. 4(6), NS Nervousness: 7(5) vs. 3(4), NS Weight Loss: 7(5) vs. 0(1), p<.05 Accidental Injury:6(5) vs. 3(4), NS Fever: 6(5) vs. 3(4), NS Gastroenteritis: 6(5) vs. 3(4), NS Somnolence: 6(5) vs. 3(4), NS Nausea: 6(5) vs. 2(3), NS	59/10	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Swanson 2006	RCT DB	Male or female patients aged 6 to 17 years who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for ADHD were eligible for enrollment. Additional inclusion criteria included a Clinical Global Impressions-Severity of Illness scale (CGI-S) rating of 4 or higher ("moderately ill" or worse), total and/or subscale cores on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version at least 1.5 standard deviations above norms for the patient's age and gender, an intelligence quotient of at least 80 as estimated by the Wechsler Intelligence Scale for Children-Third Edition, and a score of at least 80 on the Wechsler Individual Achievement Test, Second Edition, Abbreviated. Patients were eligible if they were attending a full-time school (i.e., they were not eligible if receiving home schooling) and if a teacher and parent (or legal guardian) were willing and able to participate for the duration of the study. Patients with a history or current diagnosis of pervasive developmental disorder, schizophrenia, or other psychotic disorders (DSM-IV-TR Axis I) were excluded from the study, as were those with a clinical assessment of current suicide risk or other psychiatric comorbidities requiring pharmacotherapy. To avoid potential ethical concerns, patients whose symptoms were very well controlled and who were satisfied with current therapy for ADHD (with low levels of adverse events) were also excluded, as were those who had failed to respond to 2 or more adequate courses of stimulant therapy for ADHD with trials on a range of doses and immediate- and controlled-release formations. Patients were excluded if their height or weight was below the 5th or above the 95th percentile based on National Center for Health Statistics growth charts. Additional exclusion criteria were hypertension (defined as systolic blood pressure [SBP] ≥122 mm Hg or diastolic blood pressure [DBP] ≥78 mm Hg for children aged 6-9 years; ≥126 mm Hg or ≥82 mm Hg, respectively, for ages 10-12; and ≥136 mm Hg or ≥86 mm Hg respectively, for ages 13-17), hypotension (defined as sitting SBP <50 mm Hg for children <12 years of age or <80 mm Hg for children ≥12 years of age), resting heart rate outside the range of 60 to 115 beats per minute, absolute neutrophil count below 1 x 10^9/L, history of alcohol or substance abuse, and habitual consumption of more than 250 mg/day of caffeine. Patients were not allowed to use prescription or nonprescription medications with psychotropic activity, including other treatments for ADHD and dietary supplements, within 1 week of baseline (within 2 weeks for monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) or throughout the study.	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Swanson 2006	Modafinil: Mean Dose: 395 mg Dose Range: 340 mg, 425 mg, or placebo (Titrated during first 7 - 9 days)	NR/NR	NR	Primary Outcome Measure: ADHD-RS-IV (teacher-/investigator-rated School Version) Other Measures: total, inattention, and hyperactivity-impulsivity scores on the ADHD-RS-IV School Version and the parent-/investigator-rated ADHD-RS-IV Home Version, Clinical Global Impressions-Improvement scale (CGI-I), Test of Variables of Attention (TOVA), Conners' Parent Rating Scale-Revised, Short form (CPRS:R-S), Social Skills Rating Scale (SSRS), and Child Health Questionnaire (CHQ)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Swanson 2006	Mean age= 10 yrs (Range: 6 - 17 yrs) 71% male 80% white	Modafinil vs. Placebo NS for all between group differences **CGI-S Score, N(%)** Moderately ill:117 (62) Markedly ill: 55 (29) Severely ill: 17 (9) **Current ADHD Subtype, N(%)** Inattentive: 51 (27) Hyperactive/impulsive: 10 (5) Combined: 126 (67) **Previous ADHD treatment N(%)** Total: 104 (55) Methylphenidate hydrochloride: 69 (37) Amphetamine salts: 58 (31) Atomoxetine Hydrochloride: 35 (19) Other: 12 (6) **Patients Receiving Coadministrered agents N(%)** Respiratory Agents: 20 (11) Vitamins/nutritional supplements: 5 (3) Nonopioid analgesics/anti-inflammatories: 39 (21) Antihistamines: 11 (6) Anti-infectives: 12 (6) Other: 22 (12) **ADHD-RS-IV total score, mean** School version: 37.5 Home Version: 38.8	316/NR/190	69/1/183

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Swanson 2006	Modafinil vs. placebo **ADHD-RS-IV School version** Total score: 17.1 vs. 8.2, p<.0001 Inattention: 9.4 vs. 6.6, p<.001 Hyperactivity/impulsivity: 7.7 vs. 2.8, p<.0001 **ADHD-RS-IV Home version** Total score: 13.9 vs. 7.9, p=.001 Inattention: 7.1 vs. 4.0, p<.001 Hyperactivity/impulsivity: 6.5 vs. 3.9, p=.004 **CPRS:R-S** ADHD index: 10.7 vs. 5.2, p<.001 Cognitive problems/inattention: 10.0 vs. 4.1, p<.0001 Hyperactivity: 11.8 vs. 4.6p<.001	**Modafinil vs. Placebo, N (%)** **During 7-week Double-Blind period** **Modafinil/Modafinil vs. Modafinil/placebo vs. placebo/placebo, N (%)** **During 2-week Observation period**

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Swanson 2006	**Modafinil vs. Placebo** Insomnia: 30(24) vs. 0(0), p<0.0001 Headache: 21(17) vs. 9(14) Decreased Appetite: 18(14) vs. 1(2), p=0.0042 Infection: 13(10) vs. 10(16) Abdominal Pain: 12(10) vs. 5(8) Fever: 7(6) vs. 2(3) Increased Cough: 7(6) vs. 3(5) Rhinitis: 5(4) vs. 5(8) **AE during the 2-week Observation Period Modafinil/Modafinil vs. Modafinil/Placebo vs. Placebo/Placebo** Headache: 2(5)/2(5)/0(0) Abdominal Pain: 1(2)/3(5)/1(3) Contact Dermatitis: 0(0)/2(5)/0(0)	74/12	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Biederman 2006	RCT DB	Children aged 6 to 13 years whose height and weight corresponded to greater than the fifth percentile in standardized growth charts and who were attending full-day kindergarten, elementary school, or middle school were eligible. Participants met complete criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), for ADHD (combined type, predominantly inattentive type, or predominantly hyperactive-impulsive type) at screening, as determined by a psychiatric/clinical evaluation and confirmed by the Diagnostic Interview Schedule for Children, Fourth Edition. Eligibility was restricted to those children who were stimulant-naïve (i.e., who had not received stimulant medication in the past) or who had manifested an unsatisfactory response to stimulant therapy. At screening, an intelligence quotient (IQ) of at least 80, as estimated on the Wechsler Intelligence Scale for Children, Third Edition, and a score of 80 or higher on the screener version (for learning disabilities) of the Wechsler Individual Achievement Test were used to rule out low IQ or learning disabilities as contributing causes of symptoms and were rec baseline visit, children were required to have a clinician-rated Clinical Global Impressio of Severity (CGI-S) score of 4 or more, reflecting their overall clinical condition (moderately ill or worse). For each child, availability of a parent and a weekday teacher who were willing to participate in the study was required. Main exclusion criteria include active, clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematologic, neoplastic, endocrine, neurologic, immunodeficiency, pulmonary, or other major clinical significant disorder or disease; any current psychiatric comorbidity, including but not limited to depression and other mood disorder, anxiety disorder, or pervasive mental disorder that required pharmacotherapy use of any prescription (e.g., clonidine, guanfa or nonprescription medication with psychoactive properties (e.g., over-the-counter medications or dietary supplements containing ephedrine, pseudoephedrine, caffeine, phenylpropanolamine) within 1 week of the start of the washout period; and a history or evidence of substance abuse.	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Biederman 2006	Modafinil: Dose Range: Divided doses of 300/0 (300mg/day total), 200/100 (300mg/day total), 100/200 (300mg/day total), 200/200 (400mg/day total), or placebo	7-10 day placebo run-in phase that served as a washout for those patients previously taking psychostimulants	None/NR	Primary Outcome Measure: NR Other Measures: Teacher-rated School Version and clinician-rated Home Version of the ADHD Rating Scale-IV, parent completed Conners' ADHD/DSM-IV Rating Scales (CADS-P), Clinical Global Impressions of Improvement

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Biederman 2006	Mean age=9.2 yrs (Range: 6 to 14 yrs) 75% male 81.4% caucasian	**NS for all characteristics** **Current ADHD subtype N(%)** Combined: 190 (77) Inattentive: 51 (21) Hyperactive-impulsive: 5 (2) **CGI-S N(%)** Moderately ill: 107 (43) Markedly ill: 118 (48) Severely ill: 21 (8) Among the Most Extremely ill: 2 (0.8) **ADHD—RS-IV Mean, Score** **School Version** Total: 25.6 Inattention: 14.6 Hyperactivity-impulsivity: 11.4 **Home Version** Total: 36.1 Inattention: 19.8 Hyperactivity-impulsivity: 16.2 **CADS-P, Mean, Score** (t score) Total: 74.6 ADHD Index: 73.1 Inattentive: 72.1 Hyperactive-Impulsive: 73.8	343/NR/248	22/4/196

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Biederman 2006	**RESULTS ESTIMATED FROM GRAPHIC** **Mean (SEM) Changes From Baseline to the Final Visit on ADHD Rating Scales for the 300-mg Modafinil dosing groups. (MG) 300/0 vs. 200/100 vs. 100/200 vs. Placebo (p value)** **ADHD-RS-IV, School Version** Total: -8.7(≤.01)/-7.9(<.05)/-5.3(NS)/-2.1(NS) Inattention: -4.8(≤.01)/-4(NS)/-2.7(NS)/-.5(NS) Hyperactivity-impulsivity: -4(<.05)/-3.9(<.05)/-2.7(NS)/-1.2(NS) **ADHD-RS-IV, Home Version** Total: -11.4(≤.001)/-8.1(NS)/-8(NS)/-3.8(NS) Inattention: -6(≤.01)/-4.1(NS)/-4.3(NS)/2(NS) Hyperactivity-impulsivity: -6.7(≤.001)/-4(<.05)/-3.8(NS)/-1.8(NS) **CADS-P** ADHD Index: -7.9(<.05)/-4.3(NS)/-7(NS)/4(NS) Total: -7.1(≤.01)/-6.2(NS)/-7.9(≤.01)/-2(NS) Inattentive: -7(<.05)/-4.8(NS)/-6.4(<.05)/-2.9(NS) Hyperactive-impulsive: -6.4(<.05)/-7(<.05)/-7(≤.01)/-1.6(NS) **Mean (SEM) Changes From Baseline to the Final Visit on ADHD Rating Scales for the 400-mg Modafinil dosing group. (Mg) 200/200 vs. Placebo (P Value)** **ADHD-RS-IV, School Version** Total: -5.4(NS) vs. -2.3(NS) Inattention: -3(NS) vs. -0.3(NS) Hyperactivity-impulsivity: -2.3(NS) vs. -2.1(NS) **ADHD-RS-IV, Home Version** Total: -10.2(.01) vs. -3.8(NS) Inattention: -5.4(.01) vs. -1.8(NS) Hyperactivity-impulsivity: -5(<.05) vs. -2(NS) **CADS-P** ADHD Index: -8.1(NS) vs. -4.1(NS) Total: -8.2(<.05) vs. -2.3(NS) Inattentive: -6.8(NS) vs. -2.9(NS) Hyperactive-impulsive: -8.8(<.05) vs. -2(NS)	monitoring reported or observed at 1-week intervals

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Biederman 2006	**(MG) 200/200 vs. 200/100 vs. 100/200 vs. 300/0 vs. Placebo** Headache: 7(14)/6(12)/6(13)/7(14)/11(22) Insomnia: 5(10)/7(14)[p<.05]/6(13)/5(10)/1(2) Infection: 3(6)/1(2)/3(6)4(8)/6(12) Pain (Abdominal): 3(6)/5(10)/6(13)/4(8)/4(8) Cough: 2(4)/2(4)/3(6)/6(12)/2(4) Rhinitis: 2(4)/0(0)/5(10)/2(4)/2(4) Decreased Appetite: 1(2)/4(8)/3(6)/6(12)/1(2) Fever: 0(0)/5(10)/5(10)/2(4)/2(4)	22/9	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Biederman 2005	RCT DB	Patients were 6 to 17 years of age and had a diagnosis of ADHD on the basis of criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) for ADHD at screening, as manifested by a psychiatric/clinical evaluation and the Diagnostic Interview Schedule for Children, Fourth Edition, with a Clinical Global Impression Severity of Illness (CGI-S) rating of 4 or higher ("moderately ill" or worse). In addition, patients were attending full-time school (ie, they were not being homeschooled); had a teacher-/investigator-rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version total and/or subscale score at least 1.5 SDs above normal values for age and gender, were between the 5th and 95th percentile for weight and height on the basis of National Center for Health Statistics guidelines, had an IQ of at least 80 as estimated by the Wechsler Intelligence Scale for Children–Third Edition, and had a score of at least 80 on the Wechsler Individual Achievement Test–Second Edition–Abbreviated. Patients were excluded when they had a history or current diagnosis of pervasive developmental diso other psychotic disorders (DSM-IV Axis I); evidence of suicide risk; current psychiatric comorbidity that required pharmacotherapy; or other active clinically significant disease To avoid potential ethical concerns, patients whose ADHD was well controlled and who were satisfied with current ADHD therapy (with low levels of side effects) were also excluded, as were those who had failed to respond to 2 or more adequate courses (dos and duration) of stimulant therapy for ADHD. Other exclusion criteria included a clinicall significant drug sensitivity to stimulants, a history of alcohol or substance abuse as defined by DSM-IV criteria, consumption of >250 mg/day caffeine, absolute neutrophil count <1 x 109/L, hypertension (systolic blood pressure [SBP] of ≥122 mm Hg or diastolic blood pressure [DBP] of ≥78 mm Hg for patients aged 6–9 years; SBP of ≥126 mm Hg or DBP of ≥82 mm Hg for patients aged 10–12 years; SBP of ≥136 mm Hg or D of ≥86 mm Hg for patients aged 13–17 years), hypotension (sitting SBP <50 mm Hg for patients younger than 12 years or <80 mm Hg for patients 12 years and older), and res heart rate outside the range of 60 to 115 beats per minute. Concomitant use of prescription or nonprescription agents with psychotropic properties, including ADHD treatments and dietary supplements, was prohibited within 1 week of the baseline visit (within 2 weeks for monoamine oxidase inhibitors and selective serotonin reuptake inhibitors) and during the study.	None

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Biederman 2005	Modafinil Mean Dose: 368.5 mg Dose Range: 170–425 mg once daily	1- to 4-week washout period prior to randomization	none/NR	Primary Outcome Measure: ADHD-RS-IV School Version total score Other Measures: subscale scores for inattention and hyperactivity-impulsivity for the ADHD-RS-IV School Version and the total, inattention, and hyperactivity-impulsivity scores on the Home Version, the Clinical Global Impression of Improvement scale (CGI-I), Conners' Parent Rating Scale–Revised, Short Form (CPRS-R:S), Social Skills Rating System (SSRS), and Child Health Questionnaire (CHQ)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Biederman 2005	Mean age=10.3 years 71% male Ethnicity NR	**No Statistically significant between-group differences were observed for any characteristic at baseline.** **CGI-S Score, N (%)** Moderately ill: 115 (47) Markedly ill: 93 (38) Severely ill: 37 (15) Among the most extremely ill: 1 (0.4) **Current ADHD subtype, N (%)** Inattentive: 94 (38) Hyperactive-Impulsive: 7 (3) Combined: 145 (59) **Previous ADHD treatment, N (%)** Methylphenidate-Methylphenidate Hydrochloride: 83 (34) Dexamphetamine Sulfate: 64 (26) Atomoxetine Hydrochloride: 35 (14) Other: 12 (5) **No previous ADHD treatment:** 133 (54) **Most frequently co-administered agents in >10% of patients N (%)** Non-opioid analgesics/Anti-inflammatories: 76 (31) Respiratory Agents: 49 (20) Anesthetics: 41 (20) Antihistamines: 34 (14) Other: 95 (39) **ADHD-RS-IV Total score Mean** School Version: 35.7 Home Version: 37.43	372/NR/248	118/7/244

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Biederman 2005	**Modafinil vs. Placebo, change (p value)** **No Statistically significant between-group differences were observed for any characteristic at baseline** **CGI-S Score, N (%)** Moderately ill: 115 (47) Markedly ill: 93 (38) Severely ill: 37 (15) Among the most extremely ill: (0.4) **Current ADHD subtype, N (%)** Inattentive: 94 (38) Hyperactive-Impulsive: 7 (3) Combined: 145 (59) **Previous ADHD treatment, N (%)** Methylphenidate-Methylphenidate Hydrochloride: 83 (34) Dexamphetamine Sulfate: 64 (26) Atomoxetine Hydrochloride: 35 (14) Other: 12 (5) **No previous ADHD treatment:** 133 (54) **Most frequently co-administered agents in >10% of patients N (%)** Non-opioid analgesics/Anti-inflammatories: 76 (31) Respiratory Agents: 49 (20) Anesthetics: 41 (17) Antihistamines: 34 (14) Other: 95 (39) **ADHD-RS-IV Total score Mean** School Version: 35.7 Home Version: 37.43 **Modafinil vs. Placebo, change (p value)** **ADHD-RS-IV School Version** Total Score: -15 vs. 7.3(<.0001) Inattention: -8.8 vs. -5.0(<.0001) Hyperactivity-impulsivity: -6.3 vs. -2.3(<.0001) **ADHD-RS-IV Home Version** Total Score: -14.3 vs. -7.0(<.0001) Inattention: -7.9 vs. 3.8(<.0001) Hyperactivity-impulsivity: -6.4 vs. -3.3(.001)	spontaneously reported

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Biederman 2005	Modafinil vs. Placebo N(%) Insomnia: 48(29) vs. 3(4), P<0.05 Headache: 32(20) vs. 12(15), NS Decreased Appetite: 26(16) vs. 3(4), P<0.05 Infection: 19(12) vs. 12(15), NS Rhinitis: 16(10) vs. 9(11), NS Pharyngitis: 14(9) vs. 5(6), NS Cough Increased: 13(8) vs. 7(9), NS Abdominal Pain: 12(7) vs. 9(11), NS Rash: 10(6) vs. 2(4), NS Vomiting: 10(6) vs. 7(9), NS Accidental Injury: 8(5) vs. 5(6), NS Nervousness: 7(4) vs. 5(6), NS Fever: 8(5) vs. 2(2), NS Pain: 8(5) vs. 1(1), NS Asthenia: 6(4) vs. 4(5), NS Somnolence: 4(2) vs. 4(5), NS	118/8	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Subgroup Comorbidity: Epilepsy			
Gross-Tsur 1997 Israel Poor	Between testing sessions: Open, unblinded, uncontrolled intervention During testing sessions: DB, single-dose crossover of methylphenidate and placebo (1/2 of children received placebo during the first testing session, and 1/2 during the second)	Children with epilepsy, aged 6.4 to 16.4 years, with a diagnosis of ADHD made by a pediatric neurologist using the criteria of the DSM-III-R, cognitive testing, and a behavioral questionnaire (Child Behavior Checklist (CBCL).	Epilepsy

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Subgroup Comorbidity: Epilepsy				
Gross-Tsur 1997 Israel Poor	First 8 weeks: antiepileptic drugs (AEDs) Second 8 weeks: AEDs+methylphenidate 0.3 mg/kg (observational study) Testing session #1 (after first eight weeks): assigned to a single dose of either methylphenidate 0.3 mg/kg or placebo Testing session #2 (after second eight weeks): crossed over to a single dose of either methylphenidate 0.3 mg/kg or placebo	NR/NR	NR	(1) neurologic examination (2) electroencephalography (3) AED trough level and 2 hours after dosing with AED and with methylphenidate or placebo (4) CPT

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroup Comorbidity: Epilepsy				
Gross-Tsur 1997 Israel Poor	Mean age=9.8 18 (60%) male Ethnicity NR	Mean IQ=92.8 Complex partial seizures=15 (50%) Primary tonic-clonic seizures=7 (23.3%) True absences=6 (20%) Multiple seizure type=2 (6.7%) Monotherapy=26 (86.7%) Combination therapy=4 (13.3%) Abnormal brain computed tomography=4 (13.3%)	NR/NR/30	NR/NR/30 for all but AED drug levels (n=27)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Subgroup Comorbidity: Epilepsy		
Gross-Tsur 1997 Israel Poor	Speed of response: MPH>placebo [F(1, 30)=10.1 (p<0.003) Performance decrement over time: less pronounced with MPH [interaction time-on-task by drug condition was F(2,60)=3.8 (P<0.03)	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroup Comorbidity: Epilepsy			
Gross-Tsur 1997 Israel Poor	AE's reported only for the observational study periods.	NR NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Subgroup Comorbidity: Tourette's Disorder/Tics			
Sverd 1992	RCT DB crossover	Boys between the ages of 6.1 and 11.9 years old. All subjects met Diagnostic and Statistical Manual (3rd ed) revised (DSM-III-R) diagnostic criteria for ADHD and either chronic motor tic disorder or Tourette disorder (established on the basis of clinical interview with the parent) and were above cut-off on two out of three parent-and teacher-completed hyperactivity/ADHD behavior rating scales.	100% ADHD and either chronic motor tic disorder or Tourette disorder Tourette disorder: definite=7(63.6%), by history=3(27.3%) Chronic motor tic disorder: definite=1(9.1%)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Subgroup Comorbidity: Tourette's Disorder/Tics				
Sverd 1992	methylphenidate (MPH): placebo, 0.1mg/kg, 0.3mg/kg, and 0.5mg/kg, bid, for 2 weeks each. * for any given 0.1mg/kg dose, the minimum=2.5mg, the maximum=20mg	at least 1 week for stimulants and 3 weeks for neuroleptic (pimozide)	NR	Physician evaluation: Yale Global Tic Severity Scale (YGTSS) and Tourette Syndrome Unified Rating Scale (TS unified RS) Clinic observation: playroom procedure Parent Rating Scale: Abbreviated Parent Rating scale (APRS), Primary Secondary Symptom Checklist (PSSC), Global Tic Rating Scale (GTRS), Peer Conflict Scale

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroup Comorbidity: Tourette's Disorder/Tics				
Sverd 1992	Mean age=8.3(1.96), range 6.1-11.9 years. Gender=11(100%) male Race: NR	Overall Impairment Rating scores from the Yale Global Tic Severity Scale: 2(18.2%): none 4(36.4%): minimal 4(36.4%): mild 1(9.1%): severe Global Severity Scores: mean=40.6(16.6), range 16-79	NR/ NR/ 11 enrolled	0/0/0

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Subgroup Comorbidity: Tourette's Disorder/Tics		
Sverd 1992	Placebo vs. 0.1mg/kg; Placebo vs. 0.3mg/kg; Placebo vs. 0.5mg/kg Physician evaluation-- a. YGTSS: NS b. TS unified RS: NS Observations-- a. % ontask: p<0.01; p<0.01; p<0.01 b. worksheets no. of completed: p<0.05; p<0.05; p<0.01 Parent rating-- a. APRS: p<0.01; NS; p<0.05 b. PSSC: NS c. GTRS: NS d. Peer Conflict Scale: p<0.05; p<0.05; p<0.05	Stimulant Site Effects Checklist (SSEC) by parents

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroup Comorbidity: Tourette's Disorder/Tics			
Sverd 1992	Placebo vs. 0.1mg/kg vs. 0.3mg/kg vs. 0.5mg/kg (no post hoc) SSEC-- a. Mood index: p=0.0086 b. Attention-arousal index: NS c. Somatic complaints index: NS d. Unusual motor movement: NS	none	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Nolan 1999	RCT DB crossover Withdrawal effect on tic disorders	Subjects were 19 children (18 boys and 1 girl) between the ages of 6.6 and 17.4 years old who met Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, diagnostic criteria for ADHD and either chronic motor tic disorder or Tourette's disorder (established based on a clinical interview with the parent). To be considered eligible for the study, each child had to be receiving maintenance stimulant drug therapy for a minimum of 1 year. (No attempt was made to determine the total number of days each child actually ingested medication.) In addition, subjects could not be receiving any other medication for ADHD, tics, or other emotional or behavioral disorders.	100% ADHD and either chronic motor tic disorder or Tourette disorder Tourette disorder: definite=11, by history=7 Chronic motor tic disorder: definite=1

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Nolan 1999	Methylphenidate: Mean dose = 26mg (SD 10mg) Dose range = 10 - 50mg Dextroamphetamine: Mean dose = NR Dose range = 10mg - 20mg	first 2 weeks: subjects received their maintenance dose as typically administered	NR/NR	Primary Outcome Measure: NR Other Measures: Clinically evaluated using Yale Global Tic Severity Scale (YGTSS), Tourette Syndrome Clinical Global Impression Scale, the Shapiro Tourette Syndrome Severity Scale, and the Tourette Syndrome Unified Rating Scale Parent evaluation using Hyperactivity Index of the Revised Conners Parent Rating Scale, the Hyperactivity and Aggression subscales of the Mother's Method for Subgrouping (MOMS) checklist, the Peer Conflict Scale, the ADHD category of the Child Symptom Inventory-3R: Parent Checklist (CSI-3R) Teacher evaluation using Abbreviated Parent-Teacher Questionnaire, IOWA Conners Teacher's Rating Scale, and the ADHD category of the CSI-3R Teacher Checklist

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Nolan 1999	Mean age=12.3 yrs (SD 3.0 yrs), range 6.6 - 17.4 yrs 95% male Ethnicity: NR	Mean (SD) **Parent ADHD Measures** CGI-3R ADHD category (>7): 10.0 (4.1) CHI (>15): 16.3 (4.7) MOMS Hyperactivity scale (>2): 3.6 (1.3) **Teacher ADHD Measures** CGI-3R ADHD category (>7):10.5 (3.5) CHI (>15): 18.2 (7.7) MOMS Haperactivity scale (>6): 9.7 (3.0) **Aggression measures** MOMS Aggression scale (>2): 2.0 (1.8) IOWA Aggression scale (>3): 5.5 (4.0) **Clinician Tic measures** YGTSS Motor Tic score:11.6 (3.7) YGTSS Phonic Tic score: 9.4 (4.9) YGTSS Overall Impairment Rating scores: 14.3 (12.7) YGTSS Global Severity score: 35.0 (17.2) Methylphenidate: 17 subjects and Dextroamphetamine: 2 subjects	NR/NR/19	NR/NR/19

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Nolan 1999	Placebo (blind) VS. Drug (blind) **Clinician Ratings** **YGTSS** Total Motor Tics: 10.1(7.2) vs. 8.3(4.4) NS Total Phonic Tics: 5.6(5) vs. 3.8(5.3) NS Overall Impairment Rating: 12.1(12.3) vs. 6.8(11.1) NS Global Severity Score: 29(19.5) vs. 19(18.4) NS **STSSS**: 1.6(1.1) vs. 1.5(1.2) NS **TS-CGI**: 2.1(.7) vs. 1.8(.9) NS **TS Unified Rating Scale** Shapiro Symptom Checklist Number of Motor Tics: 4(2.5) vs. 4(4.5) NS Number of Vocal Tics: 1.5(1.6) vs. 1.3(2.2) NS 2-Minute Tic Count Motor Tic Count: 4.3(2.9) vs. 5(4.3) NS Vocal Tic Count: .4(.8) vs. 1.2(1.8) p=.0037 **GTRS** Motor Tic Index: 2.6(1.4) vs. 2.7(1.5) NS Vocal Tic Index: 1.1(1.2) vs. 1(1.4) NS Tic Severity: 1.8(2.3) vs. 1.4(2.2) NS **CGI-OC**: 1.1(.7) vs. 1(.8) NS **Parent Ratings** GTRS Motor Tic Index: 2.5(1.4) vs. 2.9(1.7) NS Vocal Tic Index: 1.5(1.4) vs. 1.2(1.7) NS Tic Severity Index: 2(2.3) vs. 1.8(2.6) NS **Classroom Observations** Motor Tic Frequency: 20.4(13.1) vs. 17.8(13.8) NS Vocal Tic Frequency: 1(3) vs. 1(1.8) NS	parent reported

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Nolan 1999	none	none	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Allen 2005	RCT DB crossover	Study subjects were children or adolescents at least 7 years of age but less than 17 years and 6 months and weighing between 20 and 80 kg at the time informed consent was obtained. All study subjects met DSM-IV criteria for ADHD and had concurrent Tourette syndrome or chronic motor tic disorder, as diagnosed by clinical interview and examination by the investigator and confirmed by the Schedule for Affective Disorders and Schizophrenia for School-age Children–Present and Lifetime Version16 (K-SADSPL). Subjects' scores on the ADHD Rating Scale-IV-Parent Version: Investigator Administered and Scored (ADHDRS-IV-Parent:Inv) had to be at least 1.5 standard deviations above the age and sex norm for diagnostic subtype (predominantly inattentive or predominantly hyperactive–impulsive), or for the total score for the combined subtype (if DSM-IV criteria were met for the combined subtype), using published norms for the ADHDRS-IV-Parent:Inv at Visits 1 (enrollment) and 2 (randomization). Subjects' Yale Global Tic Severity Scale (YGTSS) total scores had to be at least 5 at both Visits 1 and 2. Exclusion criteria included a Children's Yale–Brown Obsessive–Compulsive Scale19 (C-YBOCS) total score 15 or diagnosis of obsessive-compulsive disorder severe enough, in the investigator's opinion, to require pharmacotherapy; a Children's Depression Rating Scale–Revised20 (CDRS-R) total score 40 or diagnosis of depression severe enough to require pharmacotherapy; a history of bipolar disorder or psychosis; seizure disorder; or current use of any psychotropic medication other than study drug.	100% ADHD and either chronic motor tic disorder, chronic vocal tic disorder or Tourette disorder {some patients list more than one diagnosis) Tourette disorder: 117 (79%) Chronic motor tic disorder: 44 (29.7%) Chronic vocal tic disorder: 26 (17.6%)
Subgroup Comorbidity: Pervasive Developmental Disorder/Autism			

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Allen 2005	Atomoxetine for up to 18 weeks: Mean Dose = 1.33 mg/kg/day (SD 0.22) Dose Range = 0.5 to 1.5 mg/kg/day (maximum total daily dose of 110 mg)	3-week dose titration phase and 2-week discontinuation period	diphenhydramine allowed for insomnia	Primary Outcome Measure: Yale Global Tic Severity Scale (YGTSS) total score Other Measures: Tic Symptom Self-Report (TSSR), CGI-Tic/Neuro-S, ADHDRS-IV-Parent:Inv, the CGI-Overall-S, and the CGI-ADHD/Psych-S (a subscale rating of the clinician's global assessment of the severity of ADHD and other psychiatric symptoms)

Subgroup Comorbidity: Pervasive Developmental Disorder/Autism

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Allen 2005	Mean age=11.2 yrs (SD 2.5 yrs), range 6.6 - 17.4 yrs 88.5% male 87.8% white	n(%), all NS ADHD subtype combined: 90(60.8), inattentive: 53 (35.8), hyperactive/impulsive: 5(3.4) Oppositiona Defiance Disorder: 32(21.6) Major Depression: 1(0.7) Generalized anxiety disorder 5(3.4) Obsessive Compulsive Disorder 4 (2.7) previous exposure to stimulant therapy 101(68.2)	166/148/148	83/2/148

Subgroup Comorbidity: Pervasive Developmental Disorder/Autism

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Allen 2005	Tics efficacy, Atomoxetine vs. Placebo, change mean Yale Global Tic Severity Scale (YGTSS) total score: -5.5 vs. -3.0, p=0.063 YGTSS Motor: -3.1 vs. -1.7, p=0.119 YGTSS Phonic: -2.4 vs. -1.3, p=0.168 TSSR: -4.7 vs. -2.9, p=0.095 CGI-Tic/Neuro-S: -0.7 vs. -0.1, p=0.002 ADHD/Behavior Efficacy, change mean ADHD-RS Total: -10.9 vs. -4.9, p=0.002 ADHD-RS Inattentive: -5.7 vs. -2.7, p=0.019 ADHD-RS hyperactive/impulsive: -5.2 vs. 2.1, p=0.002 CGI-ADHD/Psych-S, -0.8 vs. -0.3, p=0.015 CGI-Overall-S, -0.6 vs. -0.2, p=0.014	NR

Subgroup Comorbidity: Pervasive Developmental Disorder/Autism

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Allen 2005	No serious AE Atomoxetine vs. Placebo, N (%) Headache, 16 vs. 14, p=0.840 Vomiting, 12 vs. 6, p=0.211 Upper abdominal pain 7 vs. 9, p=0.601 decreased appetite 12 vs. 2, p=0.01 Cough 4 vs. 9, p=0.151 Nausea 12 vs.1, p=0.002 Fatigue 9 vs.3, p=0.131 Pharyngitis 3 vs. 9, p=0.073 Diarrhea 3 vs. 8, p=0.123	Atomoxetine vs. Placebo 50 vs. 53; 2 vs. 1 withdrawals due to AE	

Subgroup Comorbidity: Pervasive Developmental Disorder/Autism

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Posey 2007	RCT DB crossover academic outpatient clinic	To be eligible for the study, subjects had to meet DSM-IV criteria for autistic disorder, Asperger's disorder, or PDD-NOS. The Autism Diagnostic Interview-Revised (ADI-R) was administered to all subjects by raters who had successfully established research reliability as defined by the authors of the instrument. Because the ADI-R does not have specific criteria for Asperger's disorder or PDD-NOS, these diagnoses followed DSM-IV and took into account all information available to the clinical investigator (whose degree was an M.D. or Ph.D). All subjects had significant symptoms of ADHD (based on the CGI and SNAP-IV), were medically healthy, and were not taking any concomitant psychotropic drugs.	n=66 after the test phase Autism: 47 (71%) Asperger's Disorder: 5 (8%) PDD-NOS: 14 (21%)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Posey 2007	Methylphenidate: Mean Dose = NR Dose Range = 7.5 - 50 mg/day (.125, .25, and .5 mg/kg per dose)	1 week test-dose phase/None	NR	Primary Outcome Measure: ABC Hyperactivity subscale score Other Measures: Swanson, Nolan, and Pelham Questionnaire revised for DSM-IV (ADHD and ODD scales - parent and teacher ratings), CGI, and the Children's Yale-Brown Obsessive Compulsive Scales for PDD

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Posey 2007	Mean age=7.5 (SD 2.2 yrs) 89.4% male 72.7% Caucasian	**baseline severity, Mean (+/-SD)** SNAP-IV ADHD parent-rated: 39.82 (8.09) SNAP-IV Inattention parent-rated: 20.21(5.17) SNAP-IV hyperactivity/Impulsivity parent-rated: 19.61 (4.22) SNAP-IV ODD parent-rated: 9.61 (6.19) SNAP-IV ADHD teacher-rated: 37.23 (7.04) SNAP-IV Inattention teacher-rated: 19.30 (4.32) SNAP-IV hyperactivity/Impulsivity teacher-rated: 17.93 (4.81) SNAP-IV ODD teacher-rated: 8.83 (5.19) Clinician CYBOCS-PDD:13.30 (3.74)	117/NR/72	7//0/66

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Posey 2007	**Primary Outcome Measure: ABC Hyperactivity subscale score, parent-rated/teacher-rated** low dose, 23.0, p=0.03/ 22.9, p=0.03 med. dose, 20.6, p<0.001/ 23.6, p=0.008 high dose, 22.1, p=0.003/ 20.3, p=0.002 optimal dose, 17.2, p<0.001/ 20.1, p<0.001 **SNAP-IV ADHD mean parent-rated/mean teacher-rated** low dose,27.97, p=0.04/ 28.00, p=0.10 med. dose, 25.57, p<0.001/ 27.27, p=0.001 high dose, 27.79, p=0.02/ 26.12, p=0.005 optimal dose, 22.63, p<0.001/ 25.24, p=0.003 **SNAP-IV ODD parent-rated/teacher-rated** low dose, 6.77, p=0.14/ 5.89, p=0.11 med. dose, 7.02, p=0.25/ 6.65, p=0.17 high dose, 7.53, p=0.66/ 6.75, p=0.35 optimal dose, 5.86, p<0.001/ 5.61, p=0.04 **Inattention parent-rated/teacher-rated** low dose, 14.58, p=0.15/ 15.24, p=0.21 med. dose, 13.38, p<0.001/ 14.27, p<0.001 high dose, 14.30, p=0.06/ 14.67, p=0.02 optimal dose, 11.83, p<0.001/13.98, p<0.003 **SNAP-IV hyperactivity/Impulsivity parent-rated/teacher-rated** low dose, 13.39, p=0.02/ 12.76, p=0.08 med. dose, 12.19, p<0.001/ 13.00, p=0.01 high dose, 13.49, p=0.01/ 11.45, p=0.005 optimal dose, 10.80, p<0.001/11.26, p=0.005 **Clinician CYBOCS-PDD** low dose, 12.82, p=0.90 med. dose, 12.31, p=0.21 high dose, 13.02, p=0.80 optimal dose, 12.13, p=0/08	parent survey and report

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Posey 2007	NR in this secondary analysis	13/12	16 subjects were unable to tolerate the highest MPH dose and received a n additional week ot medium dose in the crossover phase

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Anonymous 2005 (RUPP)	RCT DB crossover academic outpatient clinic	Boys and girls aged 5 to 14 years, inclusive, with adiagnosis of autistic disorder, Asperger disorder, or PDD not otherwise specified (NOS) based on the criteria set forth in the DSM-IV.12 All of the subjects had to have interfering symptoms of hyperactivity and/or impulsiveness that were present for at least 6months and began prior to the age of years. The severity was confirmed by a CGI 13 severity subscale score of 4 or higher (rated “moderately ill,” taking into account all of the symptoms) and a total score of 27 or higher (item mean, 1.50 on a 0-3 metric) on both a parent-rated and teacher-rated Swanson, Nolan, and Pelham– version IV ADHD scale (items 1-18),14 with a score of at least10 on the hyperactivity-impulsivity subscale (items 10-18). Subjects were also eligible for entry if the hyperactivity-impulsivity subscale score on the Swanson, Nolan, and Pelham–version IV ADHDscale (items 10-18)wasat least15(item mean, 1.67), even in the absence of notable inattentiveness. Other eligibility criteria were the following: (1) no concurrent psychotropic medications for at least 1 to 3 weeks (1 week for stimulants and clonidine hydrochloride; 2 weeks fo antidepressants except fluoxetine and citalopram hydrobromide; 3 weeks for fluoxetine, citalopram hydrobromide, or antipsychotics) prior to baseline visit; (2) mental age of at least 18 months as determined by intelligence testing; (3) no other neuropsychiatric disorders that might require alternative medical management; (4) for subjects with a tic disorder, tic severity had to be mild or less on a CGI–severity subscale rating pertaining to tics only; (5) no significant medical condition, such as heart or liver disease, that coul make treatment with methylphenidate unsafe; (6) for subjects with a seizure disorder, n seizures in the past 6 months and a stable anticonvulsant dose for at least 1 month; (7) no hypertension; (8) no treatment with an adequate trial of methylphenidate hydrochlori (0.4 mg/kg per dose given at least twice daily for a minimum of 2 weeks) within the pas years; and (9) no history of severe adverse response to methylphenidate.	n=66 after the test phase Autism: 47 (71%) Asperger's Disorder: 5 (8%) PDD-NOS: 14 (21%)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Anonymous 2005 (RUPP)	Methylphenidate hydrochloride: Mean Dose = NR Dose Range = 7.5 to 50.0 mg/day (0.125, 0.250, and 0.500 mg/kg per dose. Each dose was received 3 times daily with the third dose sculpted to be approximately half of the earlier doses)	1 week test-dose phase/None	NR	Primary Outcome Measure: Teacher-rated hyperactivity subscale of the Aberrant Behavior Checklist Other Measures: parent-rated ABC hyperactivity subscale, CGI-I subscale score

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Anonymous 2005 (RUPP)	Mean age= 7.5 yrs (SD 2.2) 89.4% male 72.7% Caucasian	baseline severity, Mean (+/-SD) SNAP-IV ADHD parent-rated: 39.82 (8.09) SNAP-IV Inattention parent-rated: 20.21(5.17) SNAP-IV hyperactivity/Impulsivity parent-rated: 19.61 (4.22) SNAP-IV ODD parent-rated: 9.61 (6.19) SNAP-IV ADHD teacher-rated: 37.23 (7.04) SNAP-IV Inattention teacher-rated: 19.30 (4.32) SNAP-IV hyperactivity/Impulsivity teacher-rated: 17.93 (4.81) SNAP-IV ODD teacher-rated: 8.83 (5.19) Clinician CYBOCS-PDD:13.30 (3.74)	117/NR/72	7//0/66

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Anonymous 2005 (RUPP)	**ABC Hyperactivity subscale score, parent-rated/teacher-rated** low dose, 23.0, p=0.03/ 22.9, p=0.03 med. dose, 20.6, p<0.001/ 23.6, p=0.008 high dose, 22.1, p=0.003/ 20.3, p=0.002 optimal dose, 17.2, p<0.001/ 20.1, p<0.001	parent survey and report

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Anonymous 2005 (RUPP)	**Placebo vs. Low Dose vs. Medium Dose vs. High Dose, N (%)** Appetite Decrease: 2(3)/3(4.6)/16(24.2), p≤.001/12(24), p≤.01 Difficulty Falling Asleep: 1(1.5)/7(10.6), p≤.05/12(18.2), p≤.01/8(16), p≤.05 Abdominal Or Stomach Discomfort: 1(1.5)/2(3)/5(7.6)/6(12) Irritability: 2(3)/5(7.6)/8(12.1), p≤.05/5(10) Emotional Outburst: 0(0)/5(7.6)/9(13.6), p≤.01/5(10) Anxiety: 2(3)/3(4.6)/1(1.5)/4(8) Depression: 0(0)/1(1.5)/3(4.6)/4(8) Repetitive Behaviors and Thoughts: 2(3)/2(3)/4(6.1)/3(6) Self-Injury: 2(3)/1(1.5)/3(4.6)/3(6) Headache: 0(0)/2(3)/1(1.5)/3(6) Diarrhea: 4(6.1)/3(4.6)/3(4.6)/2(4) Social Withdrawal: 0(0)/2(3)/4(6.1)/2(4) Increased Motor Activity: 1(1.5)4(6.1)/1(1.5)/1(2) Bradycardia: 4(6.1)/3(4.6)/0(0)/0(0) Tiredness or Fatigue: 0(0)/1(1.5)/4(6.1)/0(0)		

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Arnold 2006	RCT DB crossover	Participants were children/adolescents ages 5 to 15 years with mental age =>18 months who had an ASD and symptoms of ADHD. They met the first four of five DSM-IV criteria for ADHD: symptom count, impairment, chronicity, and pervasiveness across settings and had to have a parent-rated symptom mean =>1.5 on either the nine inattentive or the nine hyperactive-impulsive ADHD symptoms, rated 0 to 3. Exclusion criteria included cardiovascular disease, glaucoma, unstable seizure disorder, other significant physical illness, psychosis, severe mood disorder, substance abuse, or pregnancy.	Autism Spectrum Disorders Autistic disorder: 7 (43.8%) Asperger's: 1 (6.3%) PDD-NOS: 8 (50.0%)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Arnold 2006	ATX: Mean (Highest) Dose = 44.2mg (SD 21.9) Dose Range = 20 - 100 mg Placebo: Mean (Highest) Dose = 48.0mg (SD 21.9) Dose Range = 20 - 100 mg	3-week dose titration phase with 1-week unblinded washout between crossover	all concomitant medications allowed except catecholaminergic drugs and Beta-blockers/NR	Primary Outcome Measure: ABC-H Other Measures: the other subscales of the ABC weekly, the DSM-IV ADHD symptoms rated 0 to 3 weekly, the Repetitive Behavior Scale-Revised at baseline and week 6 of each condition, and CGI-Severity (CGI-S) and CGI-I rating weekly by the prescribing psychiatrist, Continuous Performance Task, Match-to-Sample Task, Analogue Classroom Task

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Arnold 2006	Mean age= 9.26 yrs (SD 2.93) 75% male 81.3% Caucasian	ADI-R social communication impairment: 18.79 ADI-R communication impairment: 14.36 ADI-R stereotypy score: 5.86 ABC hyperactivity subscale score: 25.0 ADHD inattentive symptoms: 1.88 ADHD hyperactive-impulsive symptoms: 1.94 ADHD all 18 symptoms: 1.91 CGI SeverityL 4.69 Regular School class: 6 Regular class with full-time aid: 3 special class, home-schooled: 7	NR/NR/16	3/NR/16

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Arnold 2006	Atomoxetine vs. placebo **Abberant Behavior Checklist (ABC)** Hyperactivity: 19.31 vs. 22.37, p=0.04 ABC Irritability: 13.06 vs. 14.13, p=0.12 NS ABC Lethargy/social withdrawal: 6.50 vs. 7.43, p=0.01 ABC Stereotypy: 4.69 vs. 6.63, p=0.08 NS ABC Inappropriate Speech: 4.87 vs. 5.43, p=0.28 NS **DSM-IV symptom means** Inattentive: 11.2 vs. 13.63, p=0.053 NS Hyperactive/Impulsive: 10.40 vs.14.50, p=0.005 Oppositional/defiant: 6.07 vs. 7.25, p=0.20 NS **Repetitive Behavior Scale-Revised** Stereotypy: 5.37 vs.6.56, p=0.11 NS Self Injury: 1.88 vs.2.38, p=0.29 NS Compulsions: 3.19 vs.4.13, 0.07 NS Rituals: 7.88 vs. 9.31, p=13 NS Restrictive: 4.25 vs. 4.13, p=0.75 NS Total: 43.5 vs. 45.0, p=0.57 NS **CGI-I: 9 (56%) vs. 4 (25%)** **Continuous Performance Task:** Errors of Omission: 1.67 vs. 2.18, p=0.37 NS Errors of Commission: 0.57 vs. 0.77, p=0.18 NS Seat Movements total: 11.9 vs 12.52, p=0.65 NS **Match-to-Sample Task:** Accuracy: 8.80 vs. 8.88, p=0.64 NS Mean Delay: 2.91 vs. 2.84, p=0.84 NS Net Seat Movements: 1.67 vs. 1.75, p=0.63 NS	spontaneously reported and clinician probed weekly on 16-item AE scale

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Arnold 2006	**Atomoxetine vs. placebo no. (%)** Constipation: 5 (31) vs. 2(13), p=0.08 NS Diarrhea: 4(25) vs. 5 (31), p=0.14 NS Upset Stomach: 11(69) vs. 4(25), p=0.006 Nausea/Vomiting: 8(67) vs. 3(19), p=0.012 Dry Mouth: 4(25) vs. 4(25), p=0.38 NS Decreased Appetite: 12(75) vs. 8(50), p=0.20 NS headache: 4(25) vs. 7(44), p=0.63 NS Insomnia: 12(75) vs. 7(44), p=0.99 NS Rash 8(67) vs. 6(38), p=0.70 NS Mood Swings, irritability: 14(88) vs. 14 (81), p=0.39 NS Tiredness/fatigue:12(75) vs. 7(44), p=0.004 Racing Heart: 4(25) vs. 0, p=0.048 Restlessness: 16 (100) vs. 16(100), p=0.58 NS Tremor: 1 (6) vs. 2(13), p=1.0 NS Tics: 6(38) vs. 5(31), p=0.37 NS Dizziness; 1 (7) vs. 0, p=0.33 NS severe events: 2 vs. 4	3/NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Subgroup Comorbidity: Mental Retardation			
Varley 1982	Outpatient, randomized, DB, placebo cross-over study	Children with mild mental retardation (IQ was between 49 and 77), without phsychotic disorders or undersocialized aggressive conduct disorders, with clinical assessmemt consistent with DSM-III criteria for ADD	Mental Retardation (mild) (100%)
Gadow 1992	RCT DB crossover	Boys between the ages of 6.1 and 11.9 years old. Potential subjects had to meet Diagnostic and Statistical Manual (3rd ed) revised (DSM-III-R) diagnostic criteria for ADHD and either chronic motor tic disorder or Tourette disorder (established on the basis of clinical interview with the parent) and had to be above cut-off on two out of three Parent-and teacher-completed hyperactivity/ADHD behavior rating scales.	100% ADHD and either chronic motor tic disorder or Tourette disorder Tourette disorder: definite=7(63.6%), by history=3(27.3%) Chronic motor tic disorder: definite=1(9.1%)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Subgroup Comorbidity: Mental Retardation				
Varley 1982	MPH and placebo were in identical capsules. 21 days; drug or placebo was administered at 8 a.m. and noon. For 8 children who were MPH-naïve, doses were placebo, low =0.3 mg/kg per day, and high=0.6 mg/kg per day. 1 child taking MPH 40 mg/day had dosage of placebo, low=20 mg/ day, and high=40 mg/day. 1 child taking MPH 120 mg/day had dosage of placebo, low=60 mg/day, and high=120 mg/day.	None	NR	Parents and teachers kept daily rating of children's behavior while on the study; no cognitive and learning measures assessed. Teachers filled out the Conners' Teachers Questionnaire, and the parents filled out the Conners' Parent Questionnaire. Positive response was defined as significant improvement in the mean of the Conners' rating at either low or high dose compared to placebo.
Gadow 1992	methylphenidate (MPH): placebo, 0.1mg/kg, 0.3mg/kg, and 0.5mg/kg, bid, for 2 weeks each. * for ease of administration, individual milligram-doses were rounded off to the nearest 5mg. The upper limit for the moderate dose was 20mg.	at least 1 week for stimulants and 3 weeks for neuroleptic (pimozide)	NR	Classroom: Classroom Observation Codes Lunchroom: Code for Observing Social Activity (COSA) Playground: Code for Observing Social Activity (COSA) *Observers followed subjects while they were in the classroom, lunchroom and playground Rating Scale: Abbreviated Teacher Rating Scale (ATRS), IOWA Conners Teacher's Rating Scale, Peer Conflict Scale Global Tic Rating Scale

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroup Comorbidity: Mental Retardation				
Varley 1982	Median age = 11.33 (age range: 4.58 to 15 years) Male = 70 %	Median IQ full score: 68 (49-77 was range) Social class I: 2 (20%) Social class III: 2 (20%) Social class IV: 4 (40%) Social classV: 2 (20%)	NR/15/10	0/0
Gadow 1992	Mean age=8.3(1.96), range 6.1-11.9 years. Gender=11(100%) male Race: NR	Overall Impairment Rating scores from the Yale Global Tic Severity Scale: 2(18.2%): none 4(36.4%): minimal 4(36.4%): mild 1(9.1%): severe Global Severity Scores: mean=40.6(16.6), range 16-79 ADHD index: mean=8.7(1.77) Conners Hyperactivity index: mean=17.6(3.53) PSSC Hyperactivity subscale: mean=4.2(1.25)	NR/ NR/ 11 enrolled	0/0/0

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Subgroup Comorbidity: Mental Retardation		
Varley 1982	50% showed improvement overall. Teachers'/parents' ratings on Conners' forms indicated high dosage had significantly improved (t s = 1.83/ 2.67 and p s<0.05/ p s<0.02) children's ADD. Low dosage had ppositive but non-significant trend.	Parental reporting of side effects; they were given a list of common side effects. No significant side effects noted.
Gadow 1992	Placebo vs. 0.1mg/kg; Placebo vs. 0.3mg/kg; Placebo vs. 0.5mg/kg; 0.1mg/kg vs. 0.5mg/kg Classroom observation-- a. Interference: NS; p<0.01; p<0.01; p<0.05 b. Moter: p<0.01; p<0.01; p<0.01; p<0.05 c. Off-task: NS; NS; p<0.01; NS d. Noncompliance: p<0.01; p<0.01; p<0.01; NS Lunchroom observation-- a. Noncompliance: p<0.05; p<0.01; NS; NS b. Physical aggression: p<0.05; p<0.05; p<0.05; NS Playground observation: a. Noncompliance: p<0.05; p<0.05; p<0.05; NS b. Physical aggression: NS; p<0.05; NS; NS Rating Scales: a. ATRS: p<0.01; p<0.01; p<0.01; NS b. IOWA I-O: p<0.01; p<0.01; p<0.01; NS c. IOWA A: p<0.01; p<0.01; p<0.01; NS d. Peer Conflict: NS; NS; p<0.01; NS In classroom, vocal tics were significantly less frequent (p<0.01) on the 0.3mg/kg and the 0.5mg/kg doses compared with placebo Minimal effective dose: mean=0.26mg/kg or 8.4mg (range 0.1-0.5mg/kg or 2.5-20mg)	Stimulant Site Effects Checklist (SSEC) by parents

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroup Comorbidity: Mental Retardation			
Varley 1982	Gastrointestinal upset, nausea, decreased appetite (transient and mild) = 4 (40%) Sleeping difficulties = 2 (20%) Pulse rate increase (low dose/high dose) = +4.9 bpm/+7.2 bpm Mean Systolic blood pressure increase (low dose/high dose) = 1mm Hg/5.9 mm Hg Dyastolic blood pressure increase (low/high) = 0 mm / 3.5 mm (no subject developed an increase in either pulse or blood pressure that was greater than the normal range for their age.)	0/0	
Gadow 1992	NS in SSEC * no other side effect information	none	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Gadow 1995	RCT DB crossover	Children with ADHD and either chronic motor tic disorder or Tourette disorder were above cutoff on two out of three parent-completed and two out of three teacher-completed hyperactivity/ADHD behavior rating scale	100% ADHD and either chronic motor tic disorder or Tourette disorder Tourette disorder: definite=22(64.7%), by history=12(35.3%)
Handen 1990	RCT DB crossover	1. A score of 15 or more on the hyperactivity index of both the Conners Parent and Teacher Rating Scales. 2. A diagnosis of ADHD based on a semistructured interview with parents using DSM-III-R criteria. 3. Intellectual functioning within the mild-to-borderline range of mental retardation (IQ score 50 to 74, mean=65, EMR in class placement) as measured either by the Wechsler Intelligence Scale for Children-Revised(Full-Scale IQ Score) or the Stanford-Binet: Fourth Edition (Composite Index) 4. Adaptive functioning within the mild-to-borderline range of mental retardation as measured on the Vineland Adaptive Behavior Scale-Parent Version	100% mental retardation and ADHD

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Gadow 1995	methylphenidate (MPH): placebo, 0.1mg/kg, 0.3mg/kg, and 0.5mg/kg, bid, for 2 weeks each * for ease of administration, individual milligram-doses were rounded off to the nearest 2.5mg. The upper limit for the the 0.5mg/kg dose was 20mg.	at least 1 week for stimulants and 2 to 3 weeks for clonidine and neuroleptics	NR	Direct observations-- Classroom: Classroom Observation Codes Lunchroom: Code for Observing Social Activity (COSA) Playground: Code for Observing Social Activity (COSA) *Observers followed subjects while they were in the classroom, lunchroom and playground Physician Measures-- Yale Global Tic Severity Scale (YGTSS) and Shapiro Symptom Checklist from the Tourette Syndrome Unified Rating Scale
Handen 1990	week3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid (breakfast and lunch) for a 7-days period.	2 weeks	NR	Weekday classroom behavioral and attentional measures: Conners Teacher Rating Scale, CAP Behavior Checklist, Side Effects Checklist, Five-Minute Work Sample. Saturday laboratory program attentional and behavioral measures: Eight-Minute Work Sample, Observation of Eight-Minute Work Sample, Observation of Group Instruction, Continuous Performance Test Saturday laboratory program learning measure: Paired Associate Learning Task Saturday laboratory program social behavior measures: global ratings

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Gadow 1995	Mean age=8.8(1.9), range 6.1-11.9 years. Gender=31(91.2%) male Race: NR	NR	NR/ NR/ 34 enrolled	0/0/0
Handen 1990	Mean age= NR, range 6-9 years. Gender=11(91.7%) male Race: NR	NR	NR/ NR/ 12 enrolled	0/0/0

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Gadow 1995	Placebo vs. 0.1mg/kg; Placebo vs. 0.3mg/kg; Placebo vs. 0.5mg/kg; 0.1mg/kg vs. 0.5mg/kg Classroom observation-- a. Interference: p<0.05; p<0.05; p<0.01; p<0.05 b. Moter: p<0.05; p<0.01; p<0.01; p<0.05 c. Off-task: p<0.01; p<0.01; p<0.01; p<0.01 d. Noncompliance: p<0.01; p<0.01; p<0.01; p<0.05 e. Nonphysical aggression: NS; NS; NS; NS Lunchroom observation-- a. Noncompliance: NS; p<0.05; p<0.01; NS b. Physical aggression: NS; NS; p<0.01; NS c. Nonphysical aggression: NS; p<0.01; <0.05; NS Playground observation: a. Nonphysical aggression: p<0.01; p<0.05; p<0.05; NS School tic observations: a. Motor tic observation: p<0.05; NS; NS; NS Minimal effective dose: mean=0.29mg/kg/bid or 8.8mg (range 2.5mg-20mg)	NR
Handen 1990	0.3mg/kg vs. placebo; 0.6mg vs placebo Weekday measures: Teacher Conners-- a. Conduct problems: p<0.05; p<0.05 b. Hyperactivity: p<0.05; p<0.05 c. Inattention/ Passivity: p<0.05; NS d. hyperactivity Index: p<0.05; p<0.05 Teacher CAP-- a. Inattention: NS; p<0.05 b. Overactivity: p<0.05; p<0.05 Independent Task-- a. No. item completed: NS; NS b. % correct: NS; NS Saturday measures: Independent task-- a. No. items completed: p<0.05; NS b. % correct: NS; NS c. % on-task behavior: NS; p<0.05 d. % in-seat behavior: NS; NS e. Global restlessness: NS; p<0.05 f. Global interest: p<0.05; p<0.05 Group instruction-- a. % on-task behavior: NS; p<0.05 b. % in-seat behavior: p<0.05; p<0.05 c. Global restlessness: p<0.05; p<0.05 d. Global interest: NS; p<0.05 Individual testing-- a. CPT, % correct: NS; p<0.05 b. CPT, no. impulsive: NS; p<0.05 c. PALT, % correct: NS; NS Social interaction/play-- a. Solitary: NS; NS b. Interactivity: NS; NS c. Rough and tumble: NS; p<0.05 d. Negative: NS; p<0.05 e. Intense: NS; p<0.05 Global measure/play-- a. Active: NS; NS b. Social: NS; p<0.05 c. Aggressive: NS; NS	Reported by teachers

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Gadow 1995	NR	none	
Handen 1990	4(33.3%): drowsiness 1(8.3%): drowsiness without staring 1(8.3%): social withdrawal	none	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Handen 1991	RCT DB crossover	1. Intellectual functioning within the mild to borderline range of mental retardation (IQ 48-74, mean=64), as measured either by the Wechsler Intelligence Scale for Children-Revised (Full-Scale IQ Score) or the Stanford-Binet Intelligence Scale: Fourth Edition (Composite Index), and educable mental retardation in class placement 2. Adaptive functioning within the mild to borderline range of mental retardation, based upon the Vineland Adaptive Behavior Scale-Parent Version 3. A score of 15 or more on Hyperactivity Index of both the Conners Abbreviated Teacher Rating Scale and the Conners Abbreviated Parent Rating Scale 4. A diagnosis of ADHD based upon a semistructured interview with parents using DSM-III-R criteria	100% mental retardation and ADHD
Handen 1992	RCT DB crossover	1. A score of 15 or more on the hyperactivity index of both the Conners Parent and Teacher Rating Scales. 2. A diagnosis of ADHD based on a semistructured interview with parents using DSM-III-R criteria. 3. Intellectual functioning within the mild-to-borderline range of mental retardation as measured either by the Wechsler Intelligence Scale for Children-Revised(Full-Scale IQ Score) or the Stanford-Binet: Fourth Edition (Composite Index) 4. Adaptive functioning within the mild-to-borderline range of mental retardation as measured on the Vineland Adaptive Behavior Scale-Parent Version	100% mental retardation and ADHD

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Handen 1991	week3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid (breakfast and lunch) for a 7-days period.	2 weeks	NR	Side Effect Checklist (6 point Likert Scale) by teachers: motor movement, drowsy, sad, staring, social withdrawal, irritability, poor appetite, anxiety, dizzy, moody, high activity, stomachache, headache
Handen 1992	week3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid (breakfast and lunch) for a 7-days period.	None	NR	Weekday classroom measures: Conners Teacher Scale, Child Attention Problems (CAP), Five-minute work sample Saturday laboratory program attentional and behavioral measures: Ten-minute work sample, Observation of 10 minute work sample (academic task), Observation of group instruction (academic task), observation of arts and crafts session (nonacademic task), Continuous Performance Test (CPT), Paired Associate Learning Task (PAL), Selective Reminding Task (SRT) Saturday laboratory program social behavior measures: Playgroup observation

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1991	Mean age=8.6, range 6.7-12.1 years Gender=22(81.5%) male Race: NR	NR	NR/ NR/ 27 enrolled	13 withdrawn/ o lost to fu/ 27 analyzed
Handen 1992	Mean age=9.1, range 6-12 years Gender=10(71.4%) male Race: 6(42.9%) Africa American	Hollingshead socioeconomic status: middle- to upper-class: 7(50%) working class: 7(50%) IQ score 48 to 74, mean=65	NR/ NR/ 14 enrolled	0/0/14

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Handen 1991	18(67%) were identified as responders to methylphenidate. Placebo vs. 0.3mg/kg (N=27); Placebo vs. 0.6mg/kg (N=25) Irritability: NS; 14(51.8%): 3(12%), p<0.05 Anxiety: NS; 11(40.7%): 3(12%), p<0.05 High activity: 21(77.8%): 9(33.3%), p<0.05; 21(77.8%): 10(40%), p<0.05 *Other side effects: NS; NS Placebo vs. 0.3mg/kg (N=14); Placebo vs. 0.6mg/kg (N=14) Staring: 2.0: 0.93, p<0.05; 2.0: 0.75, p<0.05 Irritability: 1.21:0.43, p<0.05; 1.21: 0.33, p<0.05 Anxiety: 1.0: 0.86, NS; 1.0: 0.50, p<0.05 Moody: 0.79: 0.36, NS; 0.79: 0.00, p<0.05 High activity: 3.0: 1.50, p<0.05; 3.0: 0.75, p<0.05 *Other side effects: NS; NS	Side Effect Checklist (6 point Likert Scale) by teachers: motor movement, drowsy, sad, staring, social withdrawal, irritability, poor appetite, anxiety, dizzy, moody, high activity, stomachache, headache
Handen 1992	Placebo vs. 0.3mg/kg; Placebo vs. 0.6mg/kg Weekday measures: Conners Teacher Rating Scale-- a. Conduct problems: NS; NS b. Hyperactivity: NS; p<0.05 c. Inattention/passivity: p<0.05; p<0.05 d. Hyperactivity Index: NS; p<0.05 Teacher CAP Rating Scale-- a. Inattention: NS; p<0.05 b. Overactivity: NS; p<0.05 c. total: NS; p<0.05 Independent task: NS; NS Saturday measures: Conners Teacher Rating Scale-- a. Conduct problems: NS; NS b. Hyperactivity: p<0.05; NS c. Inattention/passivity: p<0.05; NS d. Hyperactivity Index: p<0.05; p<0.05 Teacher CAP Rating Scale-- a. Inattention: p<0.05; NS b. Overactivity: p<0.05; NS c. total: p<0.05; p<0.05 Independent task: NS; NS Individual testing: a. CPT correct and impulsive %: NS; NS b. PAL and SRT correct %: NS; NS	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1991	18(67%) were identified as responders to methylphenidate. Placebo vs. 0.3mg/kg (N=27); Placebo vs. 0.6mg/kg (N=25) Irritability: NS; 14(51.8%): 3(12%), p<0.05 Anxiety: NS; 11(40.7%): 3(12%), p<0.05 High activity: 21(77.8%): 9(33.3%), p<0.05; 21(77.8%): 10(40%), p<0.05 *Other side effects: NS; NS Placebo vs. 0.3mg/kg (N=14); Placebo vs. 0.6mg/kg (N=14) Staring: 2.0: 0.93, p<0.05; 2.0: 0.75, p<0.05 Irritability: 1.21:0.43, p<0.05; 1.21: 0.33, p<0.05 Anxiety: 1.0: 0.86, NS; 1.0: 0.50, p<0.05 Moody: 0.79: 0.36, NS; 0.79: 0.00, p<0.05 High activity: 3.0: 1.50, p<0.05; 3.0: 0.75, p<0.05 *Other side effects: NS; NS	13 withdrawals due to adverse events	
Handen 1992	NR	none	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Handen 1994	RCT, DB, setting: Subjects' school classroom, and a Saturday laboratory classroom	All subjects met criteria for a diagnosis of ADHD based on either (1) a score at or above the 98th percentile for age and gender on the Hyperactivity Index of both the Conners Parent and Teacher Rating Scales, or (2) a score of 15 points or more on the Hyperactivity Index of both the Conners Parent and Teacher Rating Scales.	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Handen 1994	2 doses of methylphenidate; (0.3 and 0.6mg/kg per dose) and a placebo.	NR	NR	Connors Parent Rating Scale, Connors Teacher Rating Scale, Continuous Performance Test,

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1994	n= 47 6.1 -12.5 years of age/31 males/ 33 Caucasians	Familes distributed across socioeconomic levels, using Hollingshead Four-Factor Index: 4.3% Level 1 19.1% Level 2 27.7% Level 3 10.6% Level 4	NR/NR/47 enrolled	NR/NR/47

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Handen 1994	Stepwise Multiple Regression Analyses using Parent and Demographic Information to Predict School Drug Response Outcome Variable; predictor Variable; b Coefficient; pValue ; r2 Connors Scale Hyperactivity; Sex; -5.23; .0438; .0955 Inattention; impulsivity-hyperactivity (P); .94;.0084;.1574 Conduct Problems; Sex; -5.32; .0139; .1041 No. of problems completed; Conduct Problems (P); 1.39; .0025; 0.1127 IQ; -1.04; .0075;.0026;.2629 % of problems correct Mental Age; .03; .0074; .1456 On-task (independent); -.20; .0095; .0015; .2827 Stepwise Multiple Regression Analyses Using Parent and Demographic Information to Predict Saturday Laboratory Drug Response On-task (independent); Hyperactivity index (T); -26.64; .0009; .2210 On-task (group); no variables Conners Scale Hyperactivity index; Hyperactivity Index (T); 0.83; .0021; .1912 Inattention; Hyperactivity Index (T); 0.47; .0030; .0927 Race; -4.37; .0060;.2377 Conduct Problems; Hyperactivity (T); .72; .0006; .2335 CPT % Correct; SES (Level 2); 152.97; .0481; .0841 CPT No. of Responses; Impulsivity-Hyperactivity Index (P); 5.01; .0036; .1149 Conduct Problems (T); 2.55; .0001; .2259 Race; -21.57; .0076; .3764 Conduct Problems (P); -1.08; .0239; .4486	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1994	NR	NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Handen 1995	RCT DB crossover	Children with mental retardation and ADHD served as subjects. All subjects met the following inclusion criteria: (1) a score of 15 or more on the Hyperactivity Index of both the Conners Parent and Teacher Rating Scales while off medication, and (2) intellectual functioning within the moderate to borderline range of mental retardation as measured by the Weschler Intelligence Scale for Children-Revised or the Stanford-Binet Intelligence Scale(Composite Index).	100% mental retardation and ADHD
Handen 1996	RCT DB crossover	All subjects met the following criteria: (1) a score of 15 or more on the Hyperactivity Index of both the Conners Parent and Teacher Rating Scales while off medication, and (2) intellectual functioning within the moderate range of mental retardation to borderline intellectual functioning, as measured by the Weschler-Intelligence Scale for children-revised or the Stanford-Binet Intelligence Scale-Fourth Edition (Composite Index).	100% mental retardation and ADHD

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Handen 1995	week3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid with breakfast and lunch for a 7-days period.	2 weeks	NR	Independent Play: each Saturday morning after medication. Restricted Academic Task: each Saturday afternoon after medication.
Handen 1996	week3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid with breakfast and 3.5-4 hours later with lunch for a 7-days period.	2 weeks	NR	Behavior problem checklists: teachers completed the Conners Hyperactivity Index, the Conners Inattention/Passivity Scale and the CAP Inattention scale at the end of each drug condition. Saturday laboratory measures: the Selective Remaining Task (SRT) was given during each drug condition. Weekday classroom measures: a daily 5-min work task similar to the one in the Saturday classroom was given, and the average number of problems completed and percentage correct was calculated

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1995	Age (months): mean=104, range 73-149 Gender: 11(50%) male Race: 17(77%) Caucasian, 4(18%) Black, 1(5%) Hispanic	Mean IQ =64(8.8), range 50-77 Hollingshead four-factor Index for social-economic status (Level): I -- 1(5%) II -- 5(23%) III -- 8(36%) IV -- 2(9%) V -- 6(27%)	NR/NR/22 enrolled	none/none
Handen 1996	Age (months): mean=103.93, range 73-160 Gender: 23(52.3%) male Race: 32(72.7%) Caucasian, 12(27.3%) other	Mean IQ =64.25(9.06), range 44-77 Hollingshead four-factor Index for social-economic status (Level): I -- 1(2.3%) II -- 12(27.3%) III -- 14(31.8%) IV -- 6(13.6%) V -- 11(25%)	NR/NR/44 enrolled	0/0/0

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Handen 1995	Independent Play: Intense -- 0.3mg/kg=0.6mg/kg>placebo (p=0.005) vocalization -- 0.3mg/kg=0.6mg/kg>placebo (p=0.001) movement -- 0.6mg/kg>placebo (p=0.009) noninvolved -- no difference nontoy item -- no difference toy pickup -- 0.6mg/kg>0.3mg/kg (p=0.006) toy leaves -- 0.6mg/kg>0.3mg/kg (p=0.008) length of time playing with toys (1-20s) -- no difference length of time playing with toys (20-120s) -- 0.6mg/kg>0.3mg/kg (p=0.004) length of time playing with toys (>120s) -- no difference Restricted Academic Task: on-task -- 0.3mg/kg=0.6mg/kg>placebo (p=0.001) distracted -- no difference touch toy -- 0.3mg/kg=0.6mg/kg>placebo (p=0.001) fidget -- no difference out of seat -- 0.6mg/kg>placebo, 0.6mg/kg>0.3mg/kg (p=0.001)	NR
Handen 1996	29(66%) responded to MPH (based on a 50% or greater decrease in Teacher Conners Hyperactivity Index) Weekday classroom measures: Conners Hyper. Index: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001 Conners Inatten./Pass.: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001 CAP Inattention: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001 No. Problems completed: 0.6mg/kg> placebo, p<0.05 Percentage correct: 0.3mg/kg> placebo, p<0.05 Saturday classroom measures: Conners Hyper. Index: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001 Conners Inatten./Pass.: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001 CAP Inattention: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001 No. Problems completed: 0.6mg/kg> placebo, p<0.001 Percentage correct: no sig. diff. SRT: NS	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1995	2(9%) had significant adverse medication side effects experience, so the 0.6mg/kg MPH dose was not given at 11:45am during the Saturday Laboratory program.	None. Missing data were imputed using a maximum likelihood technique	
Handen 1996	3(6.8%) had significant side effects experience (e.g., motor tics, lip smacking, headaches, dizziness, high blood pressure), so the medication was not given during one of the drug condition.	none. Missing data (4%) were imputed using mean replacement	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Handen 1997	RCT DB	An initial diagnosis of ADHD was made prior to entry into the double-blind MPH trial. This was based upon either (a) a score at or above the 98th percentile for age and gender on the Hyperactivity Index of both the Conners Parent and Teacher Rating Scales, or (b) a score of 15 points or more on the Hyperactivity Index of both the Conners Parent and Teacher Rating Scales.	mental retardation and ADHD
Handen 1999	RCT DB crossover	All subjects scored at or above the 90th percentile on both a teacher-completed Preschool Behavior Questionnaire and the Hyperactivity Index of the Conners Parent Rating Scale. In addition, all subjects had been previously evaluated by an interdisciplinary team of developmental specialists, during which time either a diagnosis of ADHD was confirmed or long-term concerns with inattention and overactivity were documented.	9(82%) ADHD, 2(18%) oppositional defiant disorder.
Handen 2000	RCT DB crossover	Children with autism/PDD serviced as subjects. The inclusion criteria were employed: (a) a score of 30 or more on a parent-completed Child Autism Rating Scale (CARS), (b) a diagnosis of Autism or Pervasive Developmental Disorder Not Otherwise Specified (PDDNOS) made by a board-certified child psychiatrist, and (c) a score of 15 points or more on the Hyperactivity Index of the Teacher Conners Rating Scale while off all psychotropic medication.	9(69%) Autistic disorder, 4(31%) Pervasive Development Disorder Not Otherwise Specified (PDDNOS)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Handen 1997	methylphenidate (MPH) *no dosage, duration and schedule information	NR	NR	Baseline Home Measures: Conner Parent Rating Scale Baseline Weekday Classroom Measures: Conners Teacher Rating Scale and Classroom Assignment 1-5 years Follow-up Measures: age, length of follow-up, classroom assignment, medication history, nonpharmacologic interventions, inpatient treatment, school suspensions, police involvement, Conners parent rating scale.
Handen 1999	week2-4: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid with breakfast and 3.5-4 hours later with lunch for a 7-days period.	1 week before intervention	NR	Preschool Classroom Measures at the last day of each phase (weekly): Conners Teacher Rating Scale, Preschool Behavior Questionnaire, Side Effects Checklist Laboratory Measures (weekly): Waiting Task, Resistance to Temptation, Play Session, Compliance Task, Clean-up Task.
Handen 2000	0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid with breakfast and 4 hours later with lunch for a 7-days period. *11 subjects received a third medication around 4pm based on the family's desire to provide medication at home.	NR	NR	Weekly after each MPH condition by teachers or program staffs: Conners Teacher Scale, IOWA Conners Teacher Rating Scale, Aberrant Behavior Checklist, Child Autism Rating Scale (CARS), Side Effect Checklist

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1997	Age (months): mean=130.4, range 86-178 Gender: 32(62.7%) male Race: 37(72.5%) Caucasian, 13(25.5%) Black, 1(2%) Hispanic	Mean IQ =64(8.6), range 48-77 Hollingshead four-factor Index for social-economic status (Level): I -- 3(5.9%) II -- 10(19.6%) III -- 14(27.5%) IV -- 6(11.8%) V -- 18(35.3%)	NR/NR/51 enrolled	0/0/0
Handen 1999	Age: mean=4.9, range 4-5.11 years Gender: 9(82%) male Race: NR	Mean IQ=60(11.6), range 40-78	NR/NR/11 enrolled	1 withdraw/ 0 lost/ 10 analyzed
Handen 2000	Age: mean=7.4, range 5.6-11.2 years Gender: 10(77%) male Race: 4(31%) Caucasian, 7(54%) African American, 2(15%) Hispanic	Mental retardation level: Severe/profound=3(23%%) Moderate=5(38%) Mild/Borderline=4(31%) Average IQ=1(8%)	NR/NR/13 enrolled	0 withdrawn / 1 lost/ 12 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Handen 1997	Initial vs. follow-up: Conduct problem (CA), p=0.041 Conduct problem (MA), p=0.097 Anxiety (CA), p=0.295 Anxiety (MA), p=0.041 Impulsivity-Hyperactivity (CA), p=0.003 Impulsivity-Hyperactivity (MA), p=0.007 Learning problem (CA), p<0.005 Learning problem (MA), p<0.005 Psychosomatic (CA), p=0.947 Psychosomatic (MA), p=0.569 Hyper. Index (CA), p<0.005 Hyper. Index (MA), p<0.005	NR
Handen 1999	8(73%) responded to the drugs (based on a 40% or more decrease in Teacher-rated Conners Hyperactivity Index and/or Hyperactive-Distractible subscale) Dull, social withdrawal, poor appetite, anxiety, and drowsiness were reported more in the drugs than placebo (mean): Dull -- placebo(0.4), 0.3mg/kg(1.5), 0.6mg/kg(2.2) Social withdrawal -- placebo(0.4), 0.3mg/kg(1.3), 0.6mg/kg(2.1) Poor appetite -- placebo(0.1), 0.3mg/kg(1.9), 0.6mg/kg(3.2) Anxiety --placebo(0), 0.3mg/kg(0.1), 0.6mg/kg(0.3) Drowsiness -- placebo(0), 0.3mg/kg(1.1), 0.6mg/kg(0.6)	Parents or teachers reported
Handen 2000	8(61.5%) were determined to be MPH responders (based on a minimum 50% decrease on the Teacher Conners Hyperactivity) Conners: 0.3mg/kg>placebo, p<0.005; 0.6mg/kg>placebo, p<0.05 IOWA: 0.3mg/kg>placebo, p<0.05 Aberrant Behavior Checklist: Irritability--NS; Lethargy--NS; Stereotypy--NS; Hyperactivity--0.6mg/kg>placebo, p<0.05 inappropriate speech--NS CARS: NS	Parents or teachers reported

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1997	NR	NR	
Handen 1999	5(4.5%) patients were reported with severe adverse side effects with 0.6mg/kg dose. Dull, social withdrawal, poor appetite, anxiety, and drowsiness were reported more in the drugs than placebo (mean): Dull -- placebo(0.4), 0.3mg/kg(1.5), 0.6mg/kg(2.2) Social withdrawal -- placebo(0.4), 0.3mg/kg(1.3), 0.6mg/kg(2.1) Poor appetite -- placebo(0.1), 0.3mg/kg(1.9), 0.6mg/kg(3.2) Anxiety --placebo(0), 0.3mg/kg(0.1), 0.6mg/kg(0.3) Drowsiness -- placebo(0), 0.3mg/kg(1.1), 0.6mg/kg(0.6)	1 (9%)	
Handen 2000	Side Effect Checklist rated by teachers	2(16.7%)	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Agarwal 2001	RCT DB, crossover. Setting: 1 clinic in a university setting in India.	Children 6-15 years with hyperkinetic disorder	100% had mental retardation, 2 (20%) had seizure disorder, 1 (10%) had congenital hypothyroidism, 5 (50%) had conduct disorder
Subgroup comorbidity: Learning disorders			
Grizenko 2006	RCT DB, crossover	Diagnoses of ADHD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSMIV), 31 that were based on clinical examination, nformation collected from different sources and a structured interview using the Diagnostic Interview Schedule for Children Version IV (DISC-IV). Children with an IQ lower than 70 on the Wechsler Intelligence scale for Children-III,32 a history of Tourette's syndrome, pervasive developmental disorder or psychosis were excluded from the study. Those with previous intolerance or allergic reaction to MPH were also excluded.	44% with learning disability and 56% without learning disability LD determined using the Wide range Achievement Test (WRAT) and if there was a difference in reading or math grade level >/= 2 years with respect to the expected grade level, the child was considered to have an LD in that subject.
Subgroup comorbidity: Disruptive Behavior Disorders			

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Agarwal 2001	Clonidine 4-, 6-, and 8-mcg/kg/day in two or three divided doses for 2 weeks each for a total period of 6 weeks than placebo for following 6 weeks. Crossover group was reversed, placebo first than clonidine.	None/one month without medication for hyperkinetic disorder	NR	The Hillside Behavior Rating Scale (HBRS); Parent symptom questionnaire (PSQ) and clinical global impression scale (CGI)
Subgroup comorbidity: Learning disorders				
Grizenko 2006	Placebo or 0.5 mg/kg of body weight of MPH divided in 2 equal doses (morning and noon)	none	NR	Primary Outcome Measure: Consensus Clinical Response Other Measures: Conners Global Index–Teacher's Version and Parent Version (CGI-T and CGI-P), Clinical Global Impression Scale, the Restricted Academic Situation Scale (RASS), the Conners' Continuous Performance Task (CPT), Wide Range Achievement Test, Revised (WRAT), and the Test de rendement pour francophones (TRF)
Subgroup comorbidity: Disruptive Behavior Disorders				

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Agarwal 2001	Age: 6-15 years (mean NR) Male: 8 (80%) Ethnicity: Study conducted in India, presume all children of Indian decent	NR	11/11/10	0/0/10
Subgroup comorbidity: Learning disorders				
Grizenko 2006	Mean Age: 9.2 yrs (Range: 6 -12 yrs) Male: 85.3% Ethnicity: NR	IQ Mean: 96.45 CBCL ext. mean: 70.0 CBCL int. mean: 63.5 RASS Mean: 43.8 CPT overall index: 10.6	NR/100/95	NR/NR/95
Subgroup comorbidity: Disruptive Behavior Disorders				

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Agarwal 2001	**Clonidine 4mcg/kg/day vs Clonidine 6mcg/kg/day vs Clonidine 8mcg/kg/day vs Placebo** PSQ factor and total mean score differences after treatment Conduct: 0.9 (6.8-5.9) vs 1.5 (6.8-5.3) vs 2.7 (6.8-4.1) vs 0.01 (6.8-6.7) Impulsive hyperactive: 1.8 (15.6-13.8) vs 4.7 (15.6-10.9) vs 7.7 (15.6-7.9) vs 0.03 (15.6-15.3) Total: 10.2 (78.7-68.5) vs 17 (78.7-61.7) vs 26.9 (78.7-51.8) vs 2.2 (78.7-76.5) HBRS mean score differences after treatment Gross-motor: 1.2 (5.1-3.9) vs 2.0 (5.1-3.1) vs 2.7 (5.1-2.4) vs 0.3 (5.1-4.8) Distractibility and concentration: 0.8 (3.5-2.7) vs 1.3 (3.5-2.2) vs 1.4 (3.5-2.1) vs 0.1 (3.5-3.4) Frustration tolerance: 0.2 (2.6-2.4) vs 0.6 (2.6-2.0) vs 0.8 (2.6-1.8) vs 0 (2.6-2.6) Cooperation: 0.6 (3.5-2.9) vs 1.1 (3.5-2.4) vs 1.1 (3.5-2.4) vs 0.1 (3.5-3.4) Interest in task: 0.4 (3.5-3.1) vs 0.7 (3.5-2.8) vs 1.0 (3.5-2.5) vs 0.2 (3.5-3.3) Impulsivity: 0.5 (3.5-3.0) vs 0.8 (3.5-2.7) vs 1.4 (3.5-2.1) vs 0 (3.5-3.5) CGI mean severity differences after treatment 0.4 (4.6-4.2) vs 1.1 (4.6-3.5) vs 1.9 (4.6-2.7) vs 0.1 (4.6-4.5)	NR
Subgroup comorbidity: Learning disorders		
Grizenko 2006	Responders=CCR of 2 or 3 and Non-responders=CCR of 0 or 1, number(%) Non-responders with LD: 19 (45) [with RD and MD: 10 (45), with RD only: 4 (33), with MD only: 5 (63)], without LD: 13 (25), p=0.034 Responders with LD: 23 (55) [with RD and MD: 12 (55), with RD only: 8 (67), with MD only: 3 (37)], without LD: 40 (75) Reading: with RD non-responders: 14(41), responders: 20(59) and without RD nonresponders: 19(31), responders 41(68), p=0.33 Math: with MD non-responders: 15(50), responders: 15(50) and without MD nonresponders: 18(28), responders 47(72), p=0.034	NR
Subgroup comorbidity: Disruptive Behavior Disorders		

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Agarwal 2001	Drowsiness (50%), drymouth (10%), anorexia (10%), drop in systolic blood pressure (decreased by 3%-8.9%) (70%).	NR	
Subgroup comorbidity: Learning disorders			
Grizenko 2006	No important AE or side effects were noted	NR; none	
Subgroup comorbidity: Disruptive Behavior Disorders			

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Newcorn 2005	RCT DB	Children and adolescents, 8 to 18 years of age, who met DSM-IV criteria for ADHD by clinical assessment and confirmed by structured interview (behavioral module of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime versions (K-SADS-PL). Patients were also required to have a symptom severity score ≥1.5 SDs above age and gender norms on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent version, investigator administered and -scored scale (ADHDRS-IV-Parent:Inv) for either the total score or the Inattentive or Hyperactive/Impulsive subscale scores, corresponding to the combined, primarily inattentive, and primarily hyperactive/impulsive subtypes of ADHD, respectively. Patients were assessed for lifetime psychiatric disorders, including ODD, by clinical history and structured interview, using the K-SADS-PL. Patients with learning disabilities were not excluded. However, patients were required to be of normal intelligence (IQ ≥80) as assessed by either the full WISC-III or the four specified subtests of the WISC-III (Block Design, Picture Arrangement, Similarities, and included any serious medical illness, comorbid psychosis or bipolar disorder, history of seizure disorder, or ongoing use of psychoactive medications other than the study drug Comorbidity was not a contraindication to participation, with the exception that children were not permitted to enroll if they were receiving treatment of a coexisting disorder tha took precedence over or otherwise mitigated their treatment for ADHD.	115 (39.3%) with ODD 178 (60.8%) without ODD

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Newcorn 2005	ATX: Fixed dosing of 0.5, 1.2, or 1.8 mg/kg/day or placebo (began treatment at 0.5 mg/kg/day. In the higher dose arms, drug was titrated with intermediate steps of 0.8 mg/kg/day and 1.2 mg/kg/day at 1-week intervals) Mean Dose = NR	initial 12- to 18-day medication washout period	NR	Primary Outcome Measure: ADHDRS-IV-Parent:Inv Other Measures: Conners' Parent Rating Scale-Revised Short Form (CPRS-R:S), the Clinical Global Impressions of Severity (CGI-ADHD-S). Child Health Questionnaire (CHQ)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Newcorn 2005	Mean Age: 11.1 yrs (Range: 8–18 yrs) Male: 72.5% Ethnicity: NR	ODD vs. non-ODD **ADHD Subtype No.(%) all NS** Hyperactive/impulsive: 5 (2.8) Inattentive: 92 (31.4) combined: 196 (66.9)	NR/NR/293	NR/NR/NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Newcorn 2005	**1.8 vs. 1.2 vs. 0.5 vs. placebo** **ADHDRS-IV-Parent Total mean change:** ODD: -13.4 (p=0.030)/-11.5(p=0.092)/-10.8(p=0.185)/-5.1 non-ODD: -13.6 (p=0.050)/-14.9(p=0.009)/-9.1(p=0.690)/-5.1 **ADHDRS-IV-Parent inattentive mean change:** ODD: -6.9 (p=0.020)/-5.7(p=0.105)/-5.4(p=0.194)/-2.2 non-ODD: -6.8 (p=0.098)/-7.8(p=0.010)/-4.8(p=0.688)/-3.1 **ADHDRS-IV-Parenthyperactive/impulsive mean change:** ODD: -6.6 (p=0.091)/-5.8(p=0.131)/-5.4(p=0.252)/-2.9 non-ODD: -6.8 (p=0.066)/-7.1(p=0.034)/-4.3(p=0.798)/-3.7 **CGI-ADHD-S mean change:** ODD: -1.2 (p=0.040)/-0.9(p=0.207)/-1.0(p=0.149)/-0.4 non-ODD: -1.3 (p=0.038)/-1.5(p=0.002)/-0.6(p=0.930)/-0.6 **CPRS-R:S, ADHD Index mean change:** ODD: -7.2 (p=0.018)/-6.6(p=0.030)/-7.5(p=0.016)/-0.3 non-ODD: -9.9 (p<0.001)/-10.0(p<0.001)/-7.0(p=0.125)/-2.4 **CPRS-R:S, oppositional mean change:** ODD: -3.4 (p=0.027)/-2.2(p=0.321)/-3.4(p=0.040)/-0.6 non-ODD: -2.3 (p=0.229)/-2.7(p=0.057)/-1.5(p=0.884)/-0.7 **CDRS-R:** ODD: -1.6 (p=0.255)/-1.9(p=0.209)/-1.4(p=0.300)/1.3 non-ODD: -2.2 (p=0.077)/-1.8(p=0.108)/0.6(p>0.999)/0.8 **Measures of QOL** **Psychosocial Summary mean change:** ODD: 10.8(p=0.003)/7.1(p=0.07)/4.4(p=0.238)/-0.4 non-ODD: 7.8(p=<.001)/5.8(p=.006)/4.5(p=0.124)/-0.9 **Behavior mean change:** ODD: 18.6(p=<.001)/13.0(p=.036)/9.1(p=.077)/-2.3 non-ODD: 14.6(p=<.001)/14.0(p=<.001)/7.5(p=0.250)/0.8 **Family Activity Mean Change:** ODD: 16.7(p=.006)/13.9(p=.021)/6.4(p=.269)/-0.9 non-ODD: 14.1(p=.094)/15.7(p=<.054)/10.6(p=0.495)/0.9 **Parent Impact-Emotional Mean Change:** ODD: 7.1(p=.955)/13.0(p=.627)/6.1(p=.269)/8.4 non-ODD: 13.8(p=.023)/9.3(p=.281)/5.4(p=.883)/0.7	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Newcorn 2005	NR	NR;NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Hazell 2006	RCT DB	Children and adolescents aged 6–15 years who met DSM-IV criteria for ADHD, as assessed by clinical interview and confirmed by a structured diagnostic interview [Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K-ADSPL)]. In addition, all patients had symptom severity at least 1.5 standard deviations above expected age and sex norms on the ADHD Rating Scale-IV (ADHD RS) for the patients' ADHD subtype (predominantly inattentive, predominantly hyperactive/impulsive, combined). Children and adolescents were randomly assigned in the double-blind, placebo-controlled relapse prevention study period if they were deemed responders to 10 weeks of open-label treatment with atomoxetine. Important exclusion criteria included a history of bipolar or psychotic illness, substance abuse, serious medical illness, use of concomitant psychoactive medications, and low IQ.	ADHD only: 236 ADHD + ODD: 179
Biederman 2007		Children and adolescents, aged 6–16, who met the criteria for ADHD in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), as confirmed by clinical assessment and structured interview [behavioral module of the Schedule for Affective Disorders and Schizophrenia for School-aged Children—Present and Lifetime Versions (K-SADS-PL)]. Subjects were required to have a symptom severity score that was at least 1.0 (study LYAW) or 1.5 (studies LYAT and LYBG) standard deviations above age and sex norms on the ADHDRS-IV parent version: investigator-administered and -scored scale (ADHDRS-IV-Parent:Inv) for either the total score or the inattention or hyperactivity/impulsivity subscale scores, corresponding to the combined, primarily inattentive, and primarily hyperactive/impulsive subtypes of ADHD, respectively. Subjects were assessed for lifetime psychiatric disorders, including ODD, by clinical history and structured interview, using the K-SADS-PL. Subjects with learning disabilities were not excluded. However, subjects were required to be of normal intelligence (IQ ≥80), as assessed by either the full Wechsler Intelligenc III), or the four specified subtests of the WISC-III (block design, picture arrangement, similarities, and vocabulary). Other exclusion criteria included any serious medical illness, comorbid psychosis, or bipolar disorder, history of a seizure disorder, or ongoing use of psychoactive medications other than the study drug. Comorbidity was not a contraindication to participation, with the exception that children were not permitted to enroll if they were receiving treatment of a coexisting disorder that took precedence over, or otherwise mitigated, their treatment for ADHD.	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Hazell 2006	ATX: Minimum dose of 0.5mg/kg/day to a maximum of 1.8 mg/kg/day Mean Dose = NR	Run-in: 10-week open-label trial to determine responsiveness and titrate optimal dose/NR	NR/NR	Primary Outcome Measure: Relative Risk of Relapse
Biederman 2007	Once-daily atomoxetine (up to 1.8 mg/kg/day) or placebo Mean Dose: NR In two of the three studies, subjects assigned to atomoxetine received 0.8 mg/kg/day in the morning for 3 days, after which the dose was increased to 1.2 mg/kg/day. In the other study, subjects assigned to atomoxetine received 0.5 mg/kg/day for 3 days, followed by 0.75 mg/kg/day for the remainder of the first week; then, the dose was increased to 1.0 mg/kg/day. After 3–4 weeks, subjects with significant residual symptoms [defined by a clinical global impressions of severity (CGI-S) score of 3 or greater] and for whom there was no safety or tolerability contraindication could have their dose increased to 1.5–1.8 mg/kg/day.			Primary Outcome Measure: ADHDRS-IV Other Measures: Conners' Parent RS, revised: short form (CPRS-R:S), which includes a subscale assessing oppositional behavior; the CGI-S, keyed to ADHD severity (CGI-ADHD-S); child health questionnaire (CHQ)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Hazell 2006	Mean Age: NR (Range: 6–15 yrs) Male: 90% Ethnicity: 98% Caucasian	ODD vs. non-ODD **ADHD Subtype, No.(% of total in ODD or non-ODD group)** Hyperactive/impulsive: 19(4.6) Inattentive: 93 (22.4) combined: 303 (73) **previous stimulant therapy, No.(% of total in ODD or non-ODD group)**: 218 (52.5)	604/NR/416	211/5/415
Biederman 2007	Mean age: 9.9 yrs 73.4% male Ethnicity: NR			

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Hazell 2006	**ADHD with ODD vs.ADHD without ODD taking Atomoxetine: RR 0.67, 95% CI 0.42-1.06** Mean days to relapse: 215 vs. 211, p=0.08 **ADHD with ODD vs.ADHD without ODD taking Placebo: RR 1.27, 95% CI 0.81-1.99** Mean days to relapse: 136 vs. 151, p=0.22	NR in this study
Biederman 2007		

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Hazell 2006	NR	211/10	original "parent study" reports detailed outcomes and safety data, Michelson et al 2004
Biederman 2007			

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Spencer 2006	RCT DB	Children and adolescents aged 6 to 17 years with ODD as defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. Key inclusion criteria included normal blood pressure (eg, within the 95th percentile for their age, height, and sex), an electrocardiographic (ECG) finding within normal range, and no comorbid illness that could affect the efficacy or tolerability of MAS XR. Patients were excluded if they had another psychiatric diagnosis (except ADHD); a diagnosis of conduct disorder; or a medical history of nonresponse to stimulant medication, seizures, tic disorder, or Tourette's syndrome.	ADHD +ODD: 235 (79.1%) ODD only: 70 (23.6%)

Subgroups: ADHD Subtypes

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Spencer 2006	MAS XR 10, 20, 30, or 40 mg/d or placebo (All doses were given in the morning. Forced-dose-titration design: in which patients randomized to the 10-mg/d group received 1 dose of 10 mg/d for 4 weeks. Patients randomized to the 20-mg/d group received 1 dose of 10 mg/d for the first week and 1 dose of 20 mg/d for the remaining weeks; patients randomized to the 30-mg/d group received 1 dose of 10 mg/d for the first week, 1 dose of 20 mg/d for the second week, and 1 dose of 30 mg/d for the remaining 2 weeks; and patients randomized to the 40-mg/d group received 1 dose of 10 mg/d for the first week, 1 dose of 20 mg/d for the second week, 1 dose of 30 mg/d for the third week, and 1 dose of 40 mg/d for the fourth week.) Mean Dose: NR	NR/1- to 4-week washout phase at beginning to stop all current psychtropic medication	bronchodilators and inhaled corticosteroids as needed, also allowed antibiotics and over-the-counter medications that do not affect blood pressure, heart rate, or central nervous system activity./NR	Primary Outcome Measure: ODD subscale of the Swanson, Nolan, and Pelham-IV (SNAP-IV) parent rating Other Measures: ODD subscale of the SNAP-IV teacher rating, the ADHD subscales of the SNAP-IV parent and teacher ratings, the Child Health Questionnaire Parent Form 50 (CHQ-PF50), the self-esteem module from the CHQ-CF87, and the Clinical Global Impressions (CGI)
Subgroups: ADHD Subtypes				

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Spencer 2006	Mean age: 10.6 yrs Male: 69.2% Ethnicity: 70.8% Caucasian 16.2% Black 6.5% Hispanic 6.5% Other	**Pure ODD**: 64 (20.8%) **ODD with comorbid ADHD: 79.2%** **Subtype, No.(% of total)** Hyperactive/impulsive: 17 (5.5) Inattentive: 49 (15.9) Combined: 186 (60.4) Not available: 56 (18.2) **Mean years since ODD diagnosis**: 1.46 (SD=2.5) **Mean years since ADHD diagnosis:** 2.52 (SD=3.3**)**	335/NR/308	46/13/297

Subgroups: ADHD Subtypes

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Spencer 2006	MAS XR 40mg vs. 30mg vs. 20mg vs. 10mg vs. placebo **ODD subscale of the (SNAP-IV) teacher rating, mean change (SD):** -0.49 (0.78) vs. -0.46 (0.57) vs. -0.45 (0.91) vs. -0.43 (0.77) vs. 0.09 (0.62) **ODD subscale of the (SNAP-IV) parent rating, LS mean difference:** -0.30 (NS) vs. -0.43(p<0.005) vs. -0.26 (NS) vs. -0.23 (NS) **ADHD subscales of the SNAP-IV parent:** improvements were significant in MAS XR 10mg (p=0.02), 30mg (p=0.002) and 40mg (p=0.009) groups compared with placebo **ADHD subscales of the SNAP-IV teacher:** improvements were significant in MAS XR 10mg (p=0.03), 30mg (p=0.01) and 40mg (p=0.006) groups compared with placebo **CGI-S, % much or very much improved** 61% (p<0.001) vs. 60.9% (p<0.001) vs. 55.4% (p<0.006) vs. 36.2% (p=0.122) vs. 26.7% **CHQ-PF50, change in positive treatment effects for patients treated with MSA XR:** Behavior, p=0.006 Self-Esteem, p=0.04 General health perceptions, p=0.037 Physical summary, p=0.009 Psychosocial summary, p=0.02	self report **severe,** if it was incapacitating and the patient was unable to engage in usual activity or work **serious** if it resulted in death, hospitalizations or significant or persistent incapacity
Subgroups: ADHD Subtypes		

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Spencer 2006	**MAS XR 40mg vs. 30mg vs. 20mg vs. 10mg vs. placebo** **No. (%)** Anorexia/Decreased Appetite: 21(34.4)/22(31.9)/22(37.9)/10(16.7)/3(5.0) Insomnia: 17(27.9)/16(23.2)/14(24.1)/8(13.3)/5(8.3) Headache: 16(26.2)/11(15.9)/10(17.2)/11(18.3)/9(15.0) Abdominal Pain: 7(11.5)/10(14.5)/6(10.3)/7(11.7)/3(5.0) Weight Loss: 9(14.8)/8(11.6)/6(10.3)/2(3.3)/0(0), p,0.001 Pharyngitis: 7(11.5)/2(2.9)/3(5.2)/6(10.0)/3(5.0) Nervousness: 5(8.2)/5(7.2)/4(6.9)/3(5.0)/0(0) Emotional Lability: 3(4.9)/6(8.7)/3(5.2)/2(3.3)/1(1.7) Accidental Injury: 4(6.6)/2(2.9)/4(6.9)/1(1.7)/3(5.0)	46/14	study reports ITT and PP results

Subgroups: ADHD Subtypes

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Gorman 2006	RCT DB crossover	Eligibility: ages 6 to 12; WISC-III (Wechsler, 1991) Full Scale IQ ≥80; no history of neurological disorder, chronic medical illness, bipolar disorder, schizophrenia, or pervasive developmental disorder; no episode of major depressive disorder in the preceding 6 months; normal/corrected vision and hearing; no current medication; and no physical disabilities. To confirm the diagnosis of ADHD, ≥6 inattention and/or hyperactivity/impulsivity symptoms on the Parent Interview for Child Symptoms-4, a semistructured DSM interview administered by the second author and ≥4 symptoms of inattention and/or ≥4 symptoms of hyperactivity/impulsivity on the teacher ADHD scale, a Likert scale comprising of 18 DSM-IV symptoms for ADHD were rquired. The count of inattention or hyperactivity/impulsivity symptoms endorsed by the parent was supplemented by up to two ADHD symptoms for each symptom cluster reported by the teacher.	ADHD subtypes: mixed: 22 (29.3%), inattentive: 19 (25.3%), control group 34 (45.3%)

Subgroups: Race

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Gorman 2006	Methylphenidate: Mean Dose: 33.1 mg/day Dose Range: Terminal daily doses from 25 to 50 mg	NR/NR	none/NR	Primary Outcome Measure: IOWA Conners scales (parent and teacher ratings) of: Inattention/Overactivity, Hyperactivity, Attention, Aggression/Oppositionality, Aggression, and Valence of interview responses/comments

Subgroups: Race

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Gorman 2006	Mean age: 9.1 yrs (Range: 6 to 12 yrs) Male: 52% Ethnicity: 91% Caucasian	**Frequency or mean** Socioeconomic status: 50.60, NS Anxiety disorders:7 lifetime affective disorder: 2 ODD:18, p<0.001 Wechsler full-scale IQ: 113.86, p<0.001 Basic Reading Skills Index: 113.44, p<0.001 Broad Mathematics Index: 115.98, p<0.001 Kaufman Test of Academic Achievement, Spelling: 107.91, p<0.001	NR/NR/75	NR/NR/NR

Subgroups: Race

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Gorman 2006	Mean change from pretrial (+/- SD) Parent ratings [placebo or matched session vs. MPH or matched session] / teacher ratings [placebo or matched session vs. MPH or matched session] **Inattention/Overactivity** Controls: 0.13(0.09) ADHD/I: -0.08 vs. -0.40 / -0.13 vs. -0.67, p<0.05 ADHD/C: -0.17 vs. -1.06 / -0.08 vs -0.94, p<0.001 **Hyperactivity** Controls: -.98(.06) ADHD/I: 0.05 vs. 0.12 / 0.08 vs. -0.13, p<0.05 ADHD/C: -0.04 vs. -0.44 / 0.11 vs -0.45, p<0.001 **Attention** Controls: .72(.06) ADHD/I: -.07 vs 0.21 / -0.17 vs 0.21, p<0.05 ADHD/C: 0.10 vs 0.49 / -0.07 vs. 0.46, p<0.001 **Aggression/Oppositionality** Controls: .25(.09) ADHD/I: 0.05 vs -0.03 / -0.10 vs -0.22, NS ADHD/C: 0.25 vs -0.47 / -0.10 vs. -0.58, p<0.001 **Aggression** Controls: .21(.06) ADHD/I: 0.03 vs 0.01 / 0.05 vs 0.04, NS ADHD/C: 0.15 vs -0.16 / -0.06 vs -0.27, p<0.001 **Valence of interview responses/comments,** ADHD/I: 0.26(.32) vs 1.10(.37) / -0.76(.42) vs 0.50(.43) ADHD/C: -0.15(.30) vs 1.80(.34) / -0.96(.39) vs 0.97(.40)	NR

Subgroups: Race

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Gorman 2006	MPH vs. Placebo, mean of body weight and counts of side effects (+/-SE) Body Weight (Kg): 36.09(1.99) vs. 36.54(2.01), p=0.18 Somatic Complaints: 1.14(.15) vs. 0.29(.10), p=0.001 Behavioral Complaints: 1.18(.19) vs. 1.30(.21), NS	NR/NR	

Subgroups: Race

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Gau 2007	RCT DB Parallel	Children and adolescents aged 6-16 years; met DSM-IV criteria for diagnosis of ADHD, confirmed by Chinese version of K-SADS-E; ADHDRS-IV-Parent Version: Investigator Administered and Scored Total Score of at least 25 for boys and 22 for girls, or greater than 12 for their diagnostic subtype at both visit 1 and visit 2; normal intelligence; no ADHD medication or completion of the washout procedures	Taiwanese children
Comorbity: Bipolar Disorder			
Scheffer 2005 U.S.	DB PCT crossover (after 8 weeks of open treatment with divalproex sodium)	Study subjects were recruited from a univeristy-based outpatient pediatric psychiatry clinic and the community. Elilgible subjects were males and females 6-17 years of age, who met the DSM-IV criteria for both bipolar I or bipolar II disorder (in either the mixed, manic, of hypomanic phase) and ADHD. All subjects had to score >= 14 on the Young Mania rating scale at baseline, to have scores exceeding 2 standard deviations from normal on the hyperactivity index of the Conners' Teachers and Parents Rating Scales, and to be of normal intelligence (IQ>70) on the basis of clinical impression or formal testing.	Bipolar I or II Disorder
Comorbidity: Anxiety Disorders			

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Gau 2007	Study period I: Medication-free screening/assessment Study period II: Atomoxetine 1.4 mg/kg QD (mean final dose) vs placebo x 6 weeks	No run-in/wash-out procedures not described	Concomitant use of other psychoactive medications not allowed	Primary: Total score of ADHDRS-IV Secondary: ADHDRS-IV Inattention and Hyperactivity/Impulsivity subscales; CGI-ADHD-S, Chinese version of Connors' Parent Rating Scale-Revised: Short Form (CPRS-R:S), Chinese version of Connors' Teacher Rating Scale-Revised: Short Form (CTRS-R:S)
Comorbity: Bipolar Disorder				
Scheffer 2005 U.S.	Adderall 5 mg po bid Placebo 4 weeks of treatment DB (A follow-up of 12 weeks of open label Adderall+divalproex after the 4 weeks of DB also briefly assessed)	NR / NR for Adderall part (2 week washout for psychotropics before the 8-week divalproex open label trial (fluoxetine=4 week washout)	Divalproex sodium given concomitantly.	Primary Outcome Measure: Clinical Global Impression Improvement (GCI-I) subscale Other Measures: Young Mania Rating Scale, Conners' Teachers and Parents Rating Scales
Comorbidity: Anxiety Disorders				

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Gau 2007	Mean age=9.2 years 89% male 100% Taiwanese	Height (cm): 133.6 Weight (kg): 31.5 Previous psychostimulants (# pts): 57.5% Family ADHD history: 15.1% ADHD Subtype Combined: 73% Inattentive: 27% Comorbid conditions ODD: 16% Conduct Disorder: 8.5% ADHDRS-IV, total score: 36.8 points CGI-ADHD-S: 5.3 CPRS-R:S, total score: 44 CTRS-R:S, total score: 30.6	NR/NR/106	8 (7.5%) withdrawn/LTFU NR/98 (92%) analyzed
Comorbity: Bipolar Disorder				
Scheffer 2005 U.S.	for DB crossover trial only, n=31 Mean age: 9.8 years 83.3% male 93.3% white 6.7% Hispanic	Mean Young Mania Rating score: 28.8 (SD: 5.2) Mixed phase: 83.3% Manic phase: 16.7% Bipolar I: 73.3% Bipolar II: 26.7%	NR / NR / 31	1 / NR / 30
Comorbidity: Anxiety Disorders				

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Gau 2007	**Atomoxetine vs placebo: Mean change scores** ADHDRS-IV Total Score: -17.3 vs -9.3, p=0.002 CGI-ADHD-S: -2 vs -1; p<0.001 CPRS-R:S Total Score: -12.8 vs -3.5; p<0.001 CTRS-R:S Total Score: -6.8 vs +0.8; p=0.028 Oppositional subscale: -0.1 vs +0.1; NS	Open-ended questions
Comorbity: Bipolar Disorder		
Scheffer 2005 U.S.	Mean score Adderall (n=14) vs placebo (n=16): At the end of the first 2 week period of the trial, CGi-I: 1.7 (SD=0.6) cs 3.4 (SD=1.0), p<0.0001 At the end of the 4 week DB trial (ie, after crossover): 1.8(SD=0.6) vs 3.7 (SD=1.0), p=NR % patients with treatment response sccording to CGI Improvement Score CGI=1 or 2): 89.6 % on Adderall vs 10 % on placebo	Side Effects Form for Children and Adolescents
Comorbidity: Anxiety Disorders		

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Gau 2007	**Atomoxetine vs placebo** Decreased appetite: 26 (36.1%) vs 5 (17.4%); p=0.02 Somnolence: 16 (22.2%) vs 3 (8.8%); NS Nausea: 12 (16.6%) vs 0; p<0.01 Cough Increased: 9 (12.5%) vs 7 (20.6%); NS Insomnia: 8 (11.1%) vs 1 (2.9%); NS Headache: 7 (9.7%) vs 2 (5.9%); NS Dizziness: 7 (9.7%) vs 1 (2.9%); NS Asthenia: 7 (9.7%) vs 0; p=0.09 Rhinitis: 6 (8.3%) vs 0; NS Abdominal pain: 6 (8.3%) vs 0; NS Pharyngitis: 5 (6.9%) vs 3 (8.8%); NS Vomiting: 5 (6.9%) vs 3 (8.8%); NS Diarrhea: 4 (5.6%) vs 0; NS Weight loss: 4 (5.6%) vs 0; NS Fever: 3 (4.2%) vs 5 (14.7%); NS	Total withdrawals: NR separated by group Withdrawals due to AE's: 1 (1.4%) vs 0; NS	
Comorbity: Bipolar Disorder			
Scheffer 2005 U.S.	4 week DB phase, which treatment not specified: Abdominal pain n=2 Diarrhea, n=1 Nausea, n=1 Appetite decrease, n=2 Headache, n=1 Drowsiness, n=2 Difficulty falling asleep, n=1 Irritability, n=1 Rash, n=1 AEs not specified for 12 week follow-up period	1 ; NR	During the 12-week follow-up period (n=23), the average dose was 14.5 mg/day
Comorbidity: Anxiety Disorders			

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Geller 2007	RCT DB Parallel	Children and adolescents ages 8 to 17 years who met DSM-IV criteria for ADHD and for at least one of the following anxiety disorders: separation anxiety disorder, generalized anxiety disorder or social phobia; at visits 2 and 3, patients must have had a total or subscale score on the ADHDRS-IV-PI of at least 1.5 SDs above age and sex norms for ADHD subtype, and a total score on the Pediatric Anxiety Rating Scale (PARS) of at least 15 (max score=25); ADHD diagnoses were confirmed clinically, and anxiety and ADHD diagnoses were confirmed using the K-SADS-PL administered to parent and child	Separation anxiety disorder, generalized anxiety disorder or social phobia
Comorbidity: MDD			
Bangs 2007	RCT DB Parallel	Adolescents aged 12-18 years who met the criteria for both ADHD and MDD per the DSM-IV as confirmed by the K-SADS-PL; score of at least 1.5 SD's above age and sex norms on ADHD-RS-IV; Children's Depression Rating Scale-Revised (CDRS-R) total score of at least 40 at every visit prior to randomization	Major Depressive Disorder

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Geller 2007	Study period I: Single-blind placebo run-in x 2 weeks Study period II: Atomoxetine 1.3 mg/kg/day (mean final dose) or placebo x 12 weeks	2-day washout prior to visit 2 (eligibility assessment of ADHD symptom severity); 2-week SB placebo run-in	NR	Primary: ADHDRS-IV-PI and PARS Secondary: Multidimensional Anxiety Scale for Children (MASC), CGI-S, CGI-I, Life Participation Scale for ADHD-Revised (LPS-ADHD-R), Child Health Questionnaire-Parent-Completed Full Length (CHQ-PF50)
Comorbidity: MDD				
Bangs 2007	Study period I: screening/baseline assessment Study period II: 1-week placebo lead-in (blinding unclear) Study period III: Atomoxetine 1.51 mg/kg QD (mean final dose) vs placebo x 9 weeks	Study period II: 1-week placebo lead-in (blinding unclear)/Washout N/A	No other psychotropics allowed	Primary: ADHDRS-IV-Parent:Inv, CDRS-R Secondary: MADRS, CGI-I, CGI-S, Young Mania Rating Scale (YMRS)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Geller 2007	Mean age= 12 years 64.8% male 80.7% white	Prior stimulant exposure: 62% ADHD subtype Combined: 75% Inattentive: 24% Hyperactive/Impulsive: 1% Height (mean cm): 150.1 Weight (mean kg): 46.8	269/NR/176	44 (25%)/1 (0.5%)/176 (100%)
Comorbidity: MDD				
Bangs 2007	Mean age=14 73% male 82% white	ADHD Subtype Combined: 43% Inattentive: 57% Prior stimulant exposure: 81% Height (cm): 163.7 Weight (kg): 61	NR/NR/141	22 (15%) withdrawn/4 (2.8%) LTFU/140 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Geller 2007	Lisdexamfetamine vs placebo Mean change from baseline ADHDRS-IV-PI: -9 vs -0.7, p<0.001 PARS: -4.5 vs -2.4, p<0.01 CGI-S: -0.9 vs -0.4; p=0.002 MASC: -4.6 vs 2.1; p=0.009 LPS-ADHD-R: 9.5 vs 3.1; p=0.002 CHQ-PF50: 6.9 vs 3.3; 0.019	Open-ended discussion at end of each visit
Comorbidity: MDD		
Bangs 2007	Atomoxeting vs placebo ADHDRS-IV-Parent: Inv Mean Change: -13.3 vs -5.1; p<0.001 CDRS-R mean change: 53.4 vs 52; NS CGI-I score of 1 or 2 (% pts): 33 (48%) vs 12 (18%); p<0.001 CGI-S score of 1 or 2 (% pts): 13 (19%) vs 7 (10%), NS	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Geller 2007	Mean weight loss (kg): -0.55 vs +1.39; p<.001 Decreased appetite: 11 (14.3%) vs 3 (3.8%); p=0.025 Headache: 11 (14.3%) vs 7 (8.8%), NS Upper abdominal pain: 9 (11.7%) vs 4 (5%), NS Vomiting: 8 (10.4%) vs 4 (5%), NS Irritability: 5 (6.5%) vs 3 (3.8%), NS Nasopharyngitis: 5 (6.5%) vs 5 (6.3%), NS Nausea: 5 (6.5%) vs 2 (2.5%), NS Cough: 4 (5.2%) vs 5 (6.3%), NS Influenza: 4 (5.2%) vs 1 (1.3%), NS Sinusitis: 4 (5.2%) vs 3 (3.8%), NS	Overall withdrawals: 12 (15%) vs 14 (16%) Withdrawals due to AE's: 1 (1%) vs 1 (1%)	
Comorbidity: MDD			
Bangs 2007	Atomoxetine vs placebo (% pts) Headache: 12 (17%) vs 7 (10%), NS Nausea: 16 (22%) vs 4%), p=0.002 Vomiting: 9 (12%) vs 6 (9%), NS Fatigue: 9 (12%) vs 3 (4%), NS Upper abdominal pain: 6 (8%) vs 5 (7%), NS Dizziness: 9 (12%) vs 2 (3%), NS Decreased appetite: 9 (12%) vs 0; p=0.003 Diarrhea: 1 (1%) vs 6 (9%), NS Influenza: 3 (4%) 4 (6%), NS Pyrexia: 2 (3%) vs 5 (7%), NS Weight decreased: 6 (8%) vs 1 (1%), NS Irritability: 4 (6%) vs 1 (1%), NS Weight increased: 1 (1%) vs 4 (7%), NS	Overall withdrawals: 13 (18%) vs 9 (13%), NS Withdrawals due to AE: 1 (1%) vs 1 (1%), NS	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Withdrawal of Medication			
Klein 1988 Poor	Randomized experimental study; unblinded	Cross-situational, pervasive hyperactive behavior of long duration. When they entered treatment, all were between the ages of 6 and 12 years, had Wechsler Intelligence Scale for Children IQs of 85 or above, were free of neurological disorders and psychosis, and had received a diagnosis of DSM-II hyperkinetic reaction of childhood	NR
Zeiner 1999 Fair	RCT, DB, crossover	a)biys between 7-12 years who fulfilled diagnostic criteria for ADHD; b) IQ of 70 or more; c) did not fulfill criteria for pervasive developmental disorder, psychosis, or mood disorder; d) did not have any acute or chronic medical or neurologic disease; and e) had never used stimulants or any other psychotropic drug	4(19%) had developmental readind disorder 5(24%) showed delayed development of motor functions 13(62%) was diagnosed as oppositional defiant disorder

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Withdrawal of Medication				
Klein 1988 Poor	Condition (A)="ON", remain "ON" a methylphenidate regimen all throughout up to 3-years, including summers Condition (B)="OFF", go "OFF" methylphenidate during each of two consecutive summers, with reinstatement between summers for up to 3 years Dosage ranges/mean dosages NR Dosing schedule NR	NR/NR	NR	NR
Zeiner 1999 Fair	Methylphenidate mean dose=22.4mg/day, range 15mg-35mg duration: 3 weeks dosage schedule: NR	NR/1 week	NR	Parental Account of Childhood Symptoms (PACS) Conners' Teacher Rating Scale (CTRS) Children's Checking Task (CCT) Continuous Performance Test (CPT) Paced Auditory Serial-Addition Task (PASAT) Maze Coordination Test (MCT) Gooved Pegboard Test (GPT) Reliable Change Index (RCI)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Withdrawal of Medication				
Klein 1988 Poor	Mean age=9 years 91% male Ethnicity NR	Height=133.4 cm Weight=27.9 kg	NR/NR/62	26 (41.9%) withdrawn/0 lost to fu/analyzed: One summer=58 (ON n=32, OFF n=26); Two summers=34 (ON n=20, OFF n=14)
Zeiner 1999 Fair	Mean age=8.8 years 100% male Ethnicity NR	NR	NR/NR/21	NR/NR/21

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Withdrawal of Medication		
Klein 1988 Poor	NR	Height and weight were obtained routinely by secretaries in all clinic children before and after the summer with a medical scale
Zeiner 1999 Fair	methylphenidate: placebo PACS hyperactivity- 3.8: 4.5, NS; PACS defiance- 7.4: 11.8, p<0.05 CTRS hyperactivity- 11.2: 16.8, p<0.0001; CTRS defiance- 10.4: 17.6, p<0.0001 CCT commission errors- 1.1: 1.0, NS; CCT omission errors- 2.7: 4.6, p<0.05 CPT commission errors- 4.6: 7.6, NS; CPT omission errors- 7.8: 13.8, p<0.05 PASAT R version- 8.8: 8.4, NS; PASAT S version- 8.2: 7.4, NS MCT dominant hand- 3.9: 12.0, p<0.05; MCT non-dominant hand- 30.8: 35.5, NS GPT dominant hand- 67.7: 74.9, p<0.05; GPT non-dominant hand- 83.7: 91.6, NS RCI showed significant improvement in methylphenidate treatment	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Withdrawal of Medication			
Klein 1988 Poor	ON vs OFF, t-score, p-value <u>Height (cm)</u> One summer: 134.3 vs 134.4, t=0.73, p=NS Two summers: 138.3 vs 139.8, t=2.57, p=0.02 <u>Weight (kg)</u> One summer: 28.6 vs 29.5, t=2.98, p=0.005 Two summers: 32.2 vs 32.8, t=0.88, p=NS	NR	Retrospective analysis of height/weight data from a study designed to measure efficacy
Zeiner 1999 Fair	NR	NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Sleator 1974 Poor	Long-term continuous follow-up	Children who had previously been in a DB, placebo-controlled study. These children scored >=15 (2 standard deviations above the mean) on the Conners' Teacher Abbreviated Symptom Questionnaire (ASQ) (the highest possible score is 30 and represents a maximum of hyperactive behavior).	NR
Arnold 2004 Poor	RCT placebo controlled withdrawal Setting: 7-center US	Children and adolescents with ADHD based on DSM-III-R	d-MPH: placebo ADHD type Inattentive- 7(20%): 8(20%) combinded- 28(80%): 32(80%) Stimulant naïve- 29(82.9%): 25(62.5%)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment
Sleator 1974 Poor	Mean daily dose: 0.66 mg/kg or 20.5 mg (41 subjects took doses once a day, in the morning) Children were taking MPH for a year (n=29) or two years (n=13), with a month of placebo to which the teacher and subject were both blinded. MPH was usually given on school days only.	Not applicable	NR	ASQ ratings were obtained from each subject's teacher at the end of each school month. Report cards and written reports from teachers were also obtained.
Arnold 2004 Poor	Dexmethylphenidate 5-20mg/day Duration: 6 weeks	NA	NR	Swanson, Nolan and Pelham- ADHD scale (SNAP-ADHD) rated by parents

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Sleator 1974 Poor	NR	NR	NR/NR/42	NR/NR/28
Arnold 2004 Poor	MPH group: n=35 Mean age=10.1 years Gender: 85.7% male Ethnicity: 80% Caucasian, 14.3% African-American, 5.7% Hispanic Placebo group: n=40 Mean age=9.9 years Gender: 77.5% male Ethnicity: 75% Caucasian, 12.5% African-American, 12.5% Hispanic	d-MPH: placebo Teacher SNAP-ADHD- 0.7: 0.7 Parent SNAP-ADHD- 0.65: 0.55	116/89/89	5/3/75 6 with other reasons

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results	Method of adverse effects assessment
Sleator 1974 Poor	17/42 patients showed deterioration during the placebo month. Of these 17, 5 could not continue receiveing placebo for an entire month because their restlessness threatened theirsuccessful completion of the school-year, and 7 needed an increased dose over the original recommended dose to achieve scores below 15 on the ASQ. These 7 are called the "increased-dose" subgroup. The remaining 10/17 are called the "drug-benefited" group. 11/42 scored adequate functioning (ASQ score <15) during the placebo month (the "remission" group) and were thought to be be abel to function adequately once taken off medication. No significant differences were found in mean age or IQ between the children who needed treatment versus the "remission" group (no data given). Mean ASQ Rating (placebo, 0.1 mg/kg, 0.3 mg/kg, and 0.7 mg/kg): 17, 15.8, 15.0, 11.8 (estimated from graph). Mean ASQ Score (pre-placebo, placebo, postplacebo - estimated from graph): Drug-Benefited Group: 8, 17.5, 8.5 Increased Dose Group: 17, 23.8, 14 Remission Group: 7.8, 7.0, 7.7 Mean ASQ for all subjects when receiving medication (placebo eliminated) for Sep, Oct, Nov, Dec, Jan, Feb, Mar, Apr, May: 10, 9.5, 11, 12, 11, 12.5, 11.3, 11.3, 10.8 (estimated from graph)	NR
Arnold 2004 Poor	d-MPH patients continued to demonstrate the stable benefit obtained during the open-label titration phase (baseline vs. 3pm, p=0.0025), and the magnitude of the effect at 6 hours after the noon dose was similar to the effect at 3 hours (baseline vs. 6pm, p=0.038).	reported by patients

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Sleator 1974 Poor	NR	NR	
Arnold 2004 Poor	46% of d-MPH patients and 38% of placebo patients experienced at least one AE, which is generally mild.	NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Subgroup
Sleator 1974 Poor	Long-term continuous follow-up	Children who had previously been in a DB, placebo-controlled study. These children scored >=15 (2 standard deviations above the mean) on the Conners' Teacher Abbreviated Symptom Questionnaire (ASQ) (the highest possible score is 30 and represents a maximum of hyperactive behavior).	NR
Arnold 2004 Poor	RCT placebo controlled withdrawal Setting: 7-center US	Children and adolescents with ADHD based on DSM-III-R	d-MPH: placebo ADHD type Inattentive- 7(20%): 8(20%) combinded- 28(80%): 32(80%) Stimulant naïve- 29(82.9%): 25(62.5%)

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Arnold 2004 Poor	MPH group: n=35 Mean age=10.1 years Gender: 85.7% male Ethnicity: 80% Caucasian, 14.3% African-American, 5.7% Hispanic Placebo group: n=40 Mean age=9.9 years Gender: 77.5% male Ethnicity: 75% Caucasian, 12.5% African-American, 12.5% Hispanic	d-MPH: placebo Teacher SNAP-ADHD- 0.7: 0.7 Parent SNAP-ADHD- 0.65: 0.55	116/89/89	5/3/75 6 with other reasons

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Arnold 2004 Poor	d-MPH patients continued to demonstrate the stable benefit obtained during the open-label titration phase (baseline vs. 3pm, p=0.0025), and the magnitude of the effect at 6 hours after the noon dose was similar to the effect at 3 hours (baseline vs. 6pm, p=0.038).	reported by patients

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
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Arnold 2004 Poor	46% of d-MPH patients and 38% of placebo patients experienced at least one AE, which is generally mild.	NR	

Evidence Table 6. Quality of placebo-controlled trials in children

	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?**	**Reporting of attrition, crossovers, adherence, and contamination**
Atomoxetine								
Kelsey 2004	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Spencer 2002	NR	NR	No	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Michelson 2002 Newcorn 2005	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Michelson 2001 Biederman 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Michelson 2004 Hazell 2006	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Loss to follow-up: differential /high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	*External Validity* Number screened/eligible/enrolled	Exclusion criteria
Atomoxetine						
Kelsey 2004	No	No	No	Fair	260/197/197	Serious medical illness, a history of psychosis or bipolar disorder, alcohol or drug abuse within the past 3 months, and ongoing use of psychoactive medications other than the study drug
Spencer 2002	NR	No	No	Fair	409/291/291	Poor metabolizers of CYP2D6; weight < 25 kg; documented history of bipolar I or II disorder or any history of psychosis; organic brain disease or a history of any seizure disorder, were taking any psychotropic medicatin; had any history of alcohol or drug abuse within the past 3 months; significant prior or current medical conditions
Michelson 2002 Newcorn 2005	No	No	No	Fair	NR/NR171	Serious medical illness, a history of psychosis or bipolar disorder, alcohol or drug abuse within the past 3 months, and ongoing use of psychoactive medications other than the study drug
Michelson 2001 Biederman 2002	No	Yes	No	Good	381/297/297	IQ<80 as assessed by the WISC-III; serious medical illness, comorbid psychosis or bipolar disorder, history of a seizure disorder, or ongoing use of psychoactive medications other than the study drug
Michelson 2004 Hazell 2006	No	Yes	No	Fair	NR/NR/604	Bipolar disorder; psychotic illness; unstable medical illness or patients with a conditiona that would require ongoing administration of a psychoactive medication

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Atomoxetine					
Kelsey 2004	5-day washout	No	Yes	Lilly	Yes
Spencer 2002	2-week washout	No	Yes	Lilly	Yes
Michelson 2002 Newcorn 2005	5-day washout	No	Yes	Lilly	Yes
Michelson 2001 Biederman 2002	12-18 day washout	No	Yes	Lilly	Yes
Michelson 2004 Hazell 2006	Washout of at least 5 times the plasma half-life	No	Yes	Lilly	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Bupropion								
Casat 1987	NR	NR	Yes	Yes	NR	Yes	Yes	NR, NR, NR, NR
Connors 1996	NR	NR	Yes	Yes	Yes	Yes	Yes	NR, NR, NR, NR
Daviss 2001 United States Poor Quality	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, Yes, NR
Clonidine								
Singer 1995	NR	Yes	NR	No	Yes	Yes	Yes	Yes, NR, NR, NR
Hunt 1985	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Scahill 2001	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Bupropion						
Casat 1987	No	Unclear	No	Poor	NR/NR/31	IQ < 70 on WISC-R; history of seizure disorder, tic disorder, any unstable medical conditiona, and known hypersensitivity to psychotropic medications
Connors 1996	Unclear	Unclear	No	Fair	NR/NR/109	WISC-R IQ < 70; body weight < 20 kg; girls who had passed menarche; known hypersensitivity to psychotropic medications; history or presence of seizure or tic disorders
Daviss 2001 United States Poor Quality	No	Unclear	No	Poor	NR/29/25	Pervasive developmental disorders, mental retardation, bipolar disorders, psychosis, bulimia or anorexia nervosa, current alcohol or drug abuse/dependence, Tourette's disorder, and history of a seizure disorder; serious medical problems, weight M 25 kg; known hypersensitivity to bupropion; females sexually active without contraception
Clonidine						
Singer 1995	No	Unclear	No	Fair	58/37/37	NR
Hunt 1985	NR	No	No	Poor	NR/NR/12	NR
Scahill 2001	None	Yes	No	Fair	50/40/34	Evidence of current major depression, generalized anxiety disorder, separation anxiety disorder, or psychotic symptoms; WISC-R IQ < 70; prior adequate trial of guanfacine (dose of >/= 1.5 mg/day for at least 2 weeks)

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Bupropion					
Casat 1987	14-day washout	No	Yes	Burroughs-Wellcome Company	Yes
Connors 1996	14-day washout	No	Yes	NIMH grant; 2 authors are Glaxo-Wellcome scientists	Yes
Daviss 2001 United States Poor Quality	2-week single blind placebo lead in	No	Yes	Glaxo-Wellcome	Yes
Clonidine					
Singer 1995	1-week washout between periods	No	Yes	Tourette Syndrome Association and US	
Hunt 1985	NR/NR	No	Yes	NR	
Scahill 2001	Placebo washout of 7-14 days	100% guanfacine naïve	Yes	M01-RR-06022 from the Children's Clinical Research Center, mental Health Research Center grant MH-30929 and a grant from the Tourette Syndrome Association	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Greenhill 2002	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Rugino 2003	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Greenhill 2002	No	No	No	Fair	507/321/321	Exclusion criteria: comorbid psychiatric diagnosis; history of seizure, tic disorder, or family history of Tourette's syndrome; female having undergone menarche; use of amphetamines, pemoline, or an investigational drug within 30 days of study entry; concomitant use of clonidine, anticonvulsant drugs, or medications known to affect blood pressure, heart rate, or central nervous system function; hyperthyroidism or glaucoma; any concurrent chronic or acute illness (eg, allergic rhinits, severe cold) or disability that could confound the study results. Also excluded were children who had failed a previous trial of stimulants for ADHD, had required a third daily dose in the afternoon or evening, had a documented allergy or intolerance to MPH, or were living with anyone who currently had substance abuse disorder (excluding dependency).
Rugino 2003	None	No, 2 patients excluded	No	Fair	NR/NR/24	(1) acute medical or uncontrolled psychiatric illness; (2) allergy to modafinil or any of the components of the tablet; (3) mitral valve prolapse, left ventricular hypertrophy, cardiac ischemia, clinically significant cardiac arrhythmia, or history of syncope; (4) use of the following medications within 30 days before the study: psychoactive medications other than stimulants prescribed to manage ADHD, antiepileptics, or medications metabolized primarily through the hepatic cytochrome P450 system; (5) more than 3 migraine headaches within 3 months before the study; (6) female with potential of becoming pregnant during the study; (7) uncontrolled seizure disorder; (8) sleep disorder with insomnia; and (9) history of manic episodes or psychosis

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Greenhill 2002	1-week SB placebo washout - excluded any that responded to placebo during these phase	No	Yes	Celltech Pharmaceuticals, Inc.	Low relevance because of bias towards Metadate® arm by excluding 45 children who "responded" to plcaebo during washout phase.
Rugino 2003	NR/NR	NR	Yes	NR	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Gross-Tsur 1997	Non-random assignment. Methods for assignment NR	NA	n/a-crossover	Yes	NR	Yes	Yes	NR, NR, NR, NR
Tourette's Disorder								
Sverd 1992	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR
Mental Retardation								
Varley 1982	NR	NR	NR	Yes	NR	Yes	Yes	Yes, NR, NR, NR
Gadow 1992	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR
Gadow 1995	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Gross-Tsur 1997	Unclear	Yes	No	Poor	NR/NR/30	nR
Tourette's Disorder						
Sverd 1992	Unclear	Unclear	No	Fair	NR/NR/11	Children who were believed to be too severely ill, psychotic, or mentally retarded (IQ < 75), or who had a seizure disorder, major organic brain dysfunction, major medical illness, medical or other contraindication to medication (other than tics), or pervasive developmental disorder
Mental Retardation						
Varley 1982	No/No	Yes	No	Fair	15/10/10	Psychotic disorders, undersocialized aggressive conduct disorders
Gadow 1992	Unclear	Unclear	No	Fair	NR/NR/11	Children who were believed to be too severely ill; tics were the major clinical management concern; psychotic or mentally retarded (IQ < 75); seizure disorder; major organic brain dysfunction; major medical illness, medical or other contraindication to medication, or pervasive developmental disorder
Gadow 1995	Unclear	Unclear	No	Fair	NR/NR/34	Children who were believed to be too severely ill; tics were the major clinical management concern; psychotic or mentally retarded (IQ < 75); seizure disorder; major organic brain dysfunction; major medical illness, medical or other contraindication to medication, or pervasive developmental disorder

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Gross-Tsur 1997	NR/NR	NR	Yes	NR	Yes for epilepsy+ADHD populations
Tourette's Disorder					
Sverd 1992	NR/NR	No	Yes	NR	Yes
Mental Retardation					
Varley 1982	NR/NR	80% naïve	Yes	NR	
Gadow 1992	NR/NR	Unclear	Yes	Tourette Syndrome Association and NIMH grants; CIBA supplied MPH and placebo	Yes
Gadow 1995	NR/NR	Unclear	Yes	Tourette Syndrome Association and NIMH grants; CIBA supplied MPH and placebo	

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Handen 1990	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR
Handen 1991	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR
Handen 1992	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR
Handen 1994	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Handen 1990	Unclear	Unclear	No	Fair	NR/NR/12	NR
Handen 1991	Unclear	Unclear	No	Fair	NR/NR/27	Severe motor deficits; use of other medication (anticonvulsants, antipsychotics); diagnosis of major depression or psychosis
Handen 1992	Unclear	Unclear	No	Fair	NR/NR/14	NR
Handen 1994	Unclear	Unclear	No	Fair	NR/NR/47	NR

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Handen 1990	NR/NR	Unclear	Yes	Edith L. Trees Foundation and Research Advisory Committee of Children's Hospital of Pittsburgh	Yes
Handen 1991	NR/NR	No	Yes	National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation; Research Advisory Committee of Children's Hospital of Pittsburgh	Yes
Handen 1992	NR/NR	No	Yes	National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation; Research Advisory Committee of Children's Hospital of Pittsburgh	
Handen 1994	NR/NR	No	Yes	National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation; Research Advisory Committee of Children's Hospital of Pittsburgh	

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Handen 1995	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR
Handen 1996	NR	Inadequate - hospital pharmacist	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR
Handen 1997	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Handen 1999	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Handen 2000	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR
Agarwal 2001	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Withdrawal of medication								
Klein 1988	NR	NR	Yes	Yes	NR	Unblinded study	Unblinded study	Yes, NR, NR, NR
Zeiner 1999 Fair	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Handen 1995	Unclear	Yes	No	Fair	NR/NR/22	Diagnosis of autism or pervasive developmental disorder
Handen 1996	Unclear	Yes	No	Fair	NR/NR/44	Autism or pervasive developmental disorder
Handen 1997	No	Unclear	No	Fair	NR/NR/52	Autism or pervasive developmental disorder
Handen 1999	No	No	No	Fair	NR/NR/11	Autism or pervasive developmental disorder
Handen 2000	Unclear	Yes	No	Fair	NR/NR/13	NR
Agarwal 2001	No	Yes	No	Fair	NR/NR/10	NR
Withdrawal of medic						
Klein 1988	None	No	No	Poor	NR/NR/62	NR
Zeiner 1999 Fair	No	Yes	No	Fair	NR/NR/21	NR

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Handen 1995	NR/NR	No	Yes	National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation	
Handen 1996	NR/NR	No	Yes	National Institute of Child Health and Human Development; US DHHS	
Handen 1997	NR/NR	No	Yes	National Institute of Child Health and Human Development; US DHHS	
Handen 1999	NR/NR	No	Yes	Fanny Pushin Rosenberg Research Foundation	
Handen 2000	NR/NR	Unclear	Yes	Fanny Pushin Rosenberg Research Foundation	
Agarwal 2001	NR/NR	No	Yes	NR	
Withdrawal of medic					
Klein 1988	NR/NR	NR	Yes	Supported in part by Public Health Service grant MH 18579	Yes
Zeiner 1999 Fair	NR/NR	Unclear	Yes	Norwegian Medical Research Council, Norwegian Public Health Association, and the Legacy of Haldis and Josef	Yes

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Sleator 1974	n/a - nonrandomized	n/a - nonrandomized	NR	Yes	NR	Yes	Yes	NR, NR, NR, NR
Arnold 2004 Poor	NR	NR	No	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Nolan 1999	Method NR	Method NR	N/A (crossover study)	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes	No N/A No No

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Sleator 1974	NR	NR	NR	Poor	NR/NR/42	NR
Arnold 2004 Poor	No	No	No	Fair	116/89/89	Cardiovascular, renal, respiratory (other than asthma/allergy), endocrine, or immune system disease; history of substance abuse; hypersensitivity to d,l-MH or other stimulants; treatment with any investigational drug within 30 days of screening; other significant central nervous system disorders; and treatment with antidepressants, neuroleptics/antipsychotics, mood stabilizers, anticonvulsants, beeta blockers, alpha-2 agonists, other stimulants, thyroid medications, chronic oral steroids, or sedatives/hypnotics
Nolan 1999	NR	Unclear	NR	Fair	NR/NR/19	NR

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Sleator 1974	NR/NR	NR	Yes	NIMH grant; MPH supplied by Ciba-Geigy	
Arnold 2004 Poor	NR/NR	Unclear	Yes	Celgene	
Nolan 1999	2 wk run-in regular medication (methylphenidate or dextroamphetamine)	No	N/A	Tourette Syndrome Association; US Public Health Service Grant MH45358; NIMH	ADHD + Chronic Multiple Tic Disorder

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Allen 2005	Yes - computerized interactive voice response system	Yes	Yes, for most characteristics. Higher mean ADHDRS - IV - Parent: Inv total score and hyperactivity/impulsivity subscale score at baseline in amoxetine group (described in text; p values not given)	Yes	Unclear, reported as double-blind	Yes	Yes	No No No No
Arnold 2006	Method NR	Method NR	Yes, at initial randomization (crossover study)	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes	No N/A No No

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Allen 2005	No	Yes	No	Good	NR/166/148	C-YBOCS score>15 or diagnosis of OCD requiring pharmacotherapy; CDRS-R score >40 or diagnosis of depression requiring pharmacotherapy; history of bipolar disorder or psychosis; seizure disorder; use of psychotropic drug other than study drug
Arnold 2006	No	Yes	No	Good	NR/NR/16	Cardiovascular disease, glaucoma, unstable seizure disorder, other significant physical illness, psychosis, severe mood disorder, substance abuse, pregnancy

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Allen 2005	10 to 18-day screening period	NR	Yes	Eli Lilly	ADHD + Chronic Multiple Tic Disorder
Arnold 2006	1 week unblinded washout between crossovers; 2 week washout catecholaminergic psychoactive drugs at beginning of sudy	NR	N/A	Eli Lilly; General Clinical Research Center Ohio State University	ADHD + Autism Spectrum Disorders

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Anonymous 2005/Posey 2007`	Yes	Yes	No data stratified by tx group	Yes	Yes	Yes	Yes	No N/A No No
Grizenko 2006	Method NR	Method NR	Yes, at initial randomization (crossover study)	No	Unclear, reported as double-blind	Unclear, reported as double blind	Yes	No N/A No No
Spencer 2005	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes	No No No No
Gorman 2006	Method NR	Method NR	Yes except for concomitant ODD	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes	No No No No

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Anonymous 2005/Posey 2007`	No	No	No	Fair	117/72/66	Neuropsychiatric disorders requiring alternative medical management, significant medical condition (heart or liver disease), uncontrolled (<6 mos) seizure disorder, hypertension, use of methylphenidate within 2 yrs of trial, previous adverse response to methylphenidate
Grizenko 2006	No	Yes	NR	Fair	NR/NR/95	NR
Spencer 2005	No	No for efficacy: 297/308 randomized pts included in efficacy analysis; Yes for safety	No	Good	NR/335/308	Psychiatric diagnosis other than ADHD, diagnosis of conduct disorder, medical history of nonresponse to stimulant medication, seizures, tic disorder, Tourett's syndrome
Gorman 2006	No	No	Yes; 2 (one in each group)	Fair	NR/NR/75	History of neurological disorder, chronic medical illness, bipolar disorder, schizophrenia, pervasive developmental disorder, episode of major depressive disorder in the 6 months prior to study entry, current medication use, physical disabilities

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Anonymous 2005/Posey 2007`	Washout psychotropic drugs 1-3 weeks dependant on medication; 1 week test dose run-in	No	N/A	NIH, NIMH, Korczak Foundation	Pervasive Developmental Disorders + hyperactivity
Grizenko 2006	1 week run-in	Unclear	N/A	Canadian Institutes of Health Research	ADHD + learning disabilities
Spencer 2005	1-4 wk washout of current psychotropic medication and replaced with placebo	No	N/A	Shire Pharmaceuticals	ADHD + ODD
Gorman 2006	NR	No	Yes	NIMH grant # MH56571	ADHD subtypes (inattentive; combined)

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
McGough 2006	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind	No No No No
Hall 1972	Yes	Yes	Yes	Yes	Yes	Unclear, reported as double-blind	Yes	No No No No
Greenhill 2006	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind	No No No No

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
McGough 2006	No	Yes	No	Good	NR/NR/93	Cormobid psychiatric diagnosis (except ODD) history of seizures or tic disorders, mental retardation, any illness or skin disorder that might jeopardize safety or compromise study assessments.
Hall 1972	No	Yes	No	Good	40/32/32	Current medical illness or past medical history which contraindicated stimulant therapy, required other concurrent medication, free of gross organic involvement, severe recurring seizures or significant sensory and/or gross motor deficits use of phenothiazine two months preceding study entry.
Greenhill 2006	No	No	No	Fair	295/240/200	History or current diagnosis of pervasive developmental disorder, schizophrenia or other psychotic disorders, psychatric comorbidity that required pharmacotherapy, evidence of suicide risk, ADHD symptoms well controlled on current therapy with tolerable side effects, failure to respond to two or more adequate courses (dose and duration) of stimulant therapy, ANC <1x10-9th/L, hypertension, hypotension, history of alcohol or substance abuse, caffeine consumption >250mg/day

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
McGough 2006	Up to 28 days washout existing medications	No	Yes	Shire Pharmaceuticals	
Hall 1972	NR	No	Yes	Abbott Labs (partial funding)	Genera;
Greenhill 2006	MAOI and SSRI 2 wk washout; Prescription or nonprescription medications w/psychotropic properties 1 wk washout; at least 1 wk washout for all patients	No	Yes	NR	

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Swanson 2006	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes	No No No No
Biederman 2005	Yes	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes	No No No No

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Swanson 2006	No	Yes	Yes (1 pt in modafinil group)	Fair	316/232/190	History or current diagnosis of pervasive developmental disorder, schizophrenia or other psychotic disorders, suicide risk, other psychiatric comorbidities requiring pharmacotherapy, well controlled ADHD , previous failure to respond to 2 or more adequate courses of stimulant therapy for ADHD, height or weight below 5th or above 95th percentile
Biederman 2005	No	No	Yes (2 in placebo group)	Fair	372/281/248	History or current diagnosis of pervasive developmental disorder, schizophrenia, other psychotic disorders, suicide risk, current psychiatric comorbidity requiring pharmacotherapy, other active clinically significant disease, well controlled ADHD, previous failure to respond to 2 or more adequate courses of stimulant therapy, clinically significant drug sensitivity to stimulants, history of alcohol or substance abuse, consumption of >250 mg caffeine/day, ANC <1x10-9th/L, hypertension, hypotension, resting heart rate 60-115 bpm

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Swanson 2006	Prior ADHD medication 1-4 wk washout	No	Yes	Cephalon Inc	
Biederman 2005	MAOI and SSRI 2 wk washout; Prescription or nonprescription medications w/psychotropic properties 1 wk washout; at least 1 wk washout for all patients	No	Yes	Cephalon Inc	

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Biederman 2006	Method NR	Method NR	No - due to prespecified randomization procedure, pts randomized to modafinil 400 mg had higher body weight and were older (in text; p values NR)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes	No No No No
Greenhill 2006	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind	No No No No
Silva 2006	Yes	Method NR	Yes (reported in text; no comparative table)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes	No No No No

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Biederman 2006	No	Yes	No	Good	343/NR/248	Active, clinically significant GI, CV, hepatic, renal, hematologic, neoplastic, endocrine, immunodeficiency, pulmonary or other major clinically significant disorder or disease, current psychiatric comorbidity including depression or other mood disorder, anxiety disorder, pervasive mental disorder requiring pharmacotherapy, use of any prescription medication with psychoactive properties w/in 1 wk of study entry, history or evidence of substance abuse
Greenhill 2006	No	No	No	Fair	NR/NR/103	Clinically significant abnormalities in vital signs, physical examinations, laboratory tests, history of seizures or use of anticonvulsants, comorbid psychiatric conditions, any medical condition that could interfere with study participation or assessments or that may pose a danger with administration of methylphenidate, use of psychtropic medications, initiation of psychotherapy within 3 mos, positive urine drug screen, histoyr of poor response or intolerance to methylphenidate, pregnant/nursing, use of other investigational drug w/in 30 days of current study
Silva 2006	No	Yes	No	Fair	54/54/54	Below average IQ at screening or preexisting evidence of IQ <80, home schooled, diagnosis of Tourette's or tic disorder, concurrent history of significant medical or psychiatric illness , substance abuse disorder, parents/guardians unable to understand or follow instructions

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Biederman 2006	7-10 day placebo washout	Yes	Yes	Cephalon Inc	
Greenhill 2006	At least 7 days washout exisitng ADHD therapy	No	Yes	Novartis Pharmaceuticals Corporation	
Silva 2006	NR	No	Yes	Novartis Pharmaceuticals Corporation	

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Bangs 2007	Method NR	Method NR	yes	yes	Unclear, reported as double-blind	Unclear, reported as double blind	Unclear, reported as double-blind	Yes, NR, NR, NR
Geller, 2007	Method NR	Method NR	Unclear - some differences, other important parameters not reported	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Unclear, reported as double-blind	Yes, NR, NR, NR
Gau, 2007	Method NR	Method NR	Unclear - typographical error in table makes interpretation difficult; some differences exist	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes, NR, NR, NR

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Bangs 2007	15.5% overall; 12.9% placebo, 18.1 ATM	1 patient of 142 total excluded from analysis	no	Fair	NR/NR/142	Beginning structured psychotherapy for ADHD and/or depression less than 1 month before trial entry
Geller, 2007	Yes - 25% overall; not differentiail	Yes, using LOCF	No	Poor	269/NR/176	Significant abnormalities in baseline laboratory or ECT results; met diagnostic criteria for current PTSD, panic disorder, specific phobias, or OCD; scored 15 or greater on CYBOCS; history of hypertension or bipolar, psychotic, pervasive developmental or seizure disorders; pregnant and lactating females, use of MAOI's within 2 weeks of visit 2, recent substance abusers, serious suicidal risk or with medical or personal conditions likely to affect the trial or health outcomes; cc use of drugs that inhibit the CYP2D6 enzyme pathway
Gau, 2007	No	Stated ITT in methods, but unclear in results	No	Fair	NR/NR/106	Weight less than 20 kg or more than 60 kg; serious medical illness, such as a CV disease; history of bipolar I or II disorder, psychosis, or PDD; DSM-IV anxiety disorder at study entry; history of seizure disorder or prior EEG abnormalities related to epilepsy, or had taken/were taking anticonvulsants for seizure control; history of alcohol or drug abuse within past 3 months; potential for need for other psychoactive medications other than theh study drug during the study period

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Bangs 2007	1 week placebo lead-in (blinding unclear); washout N/A	No	Yes	Eli Lilly & Company	Comorbid MDD
Geller, 2007	14 d placebo run-in resulted in 18 exclusions	No, some difference in groups as well	Unclear	Eli Lilly & Company	Children with comorbid anxiety disorder with parents familiar with ADHD behaviors in school
Gau, 2007	No/No	No	Yes	Eli Lilly & Company	Taiwanese children

Evidence Table 6. Quality of placebo-controlled trials in children

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?	Reporting of attrition, crossovers, adherence, and contamination
Biederman 2007	Method NR	Method NR	N/A (crossover study)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes, NR, NR, NR

Evidence Table 6. Quality of placebo-controlled trials in children

					External Validity	
Author, Year Country	**Loss to follow-up: differential /high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Biederman 2007	No/No	4% excluded	No	Fair	NR/52/52	Presence of comorbid illness that could interfere with study participation or impact the efficacy and tolerabilitiy of LDX or MAS XR; documented allergy or intolerance to MAS XR; drug abuse history; concomitant medications with CNS effects; history of seizures with last 2 years, tic disorders, hyperthyroidism, cardiac disorders, significant laboratory abnormalities

Evidence Table 6. Quality of placebo-controlled trials in children

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Biederman 2007	3 weeks of open MAS XR; no washout between treatment periods	No	Yes	New River Pharmaceuticals and Shire	Yes

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
PCT > 6 mos			
DEX			
Conrad 1971 (Poor)	children from low-income neighborhood, in grades kindergarten-second grade, with rating from teacher as hyperactive (19th percentile or lower), and with sings of significant perceptual-cognitive impairment as defined by: perceptual age one year or more below on Bender-Gestalt, Frostig Percpetual Quotient of 90 or less, 3 or more errors on Bender-Gestalt, discrepancy between verbal IQ and Performance IQ on WISC of 15 or more points, variablity maong subscores on WISC of 6 or more points	NR	n=68 randomized into 1 of 4 groups: Grp A: placebo/no tutoring (n=18) Grp B: placebo/tutoring (n=17) Grp C: dextroamphetamine/no tutoring (n=17) Grp D: dextroamphetamine/tutoring (n=16) duration 4-6 months doses increased/decreased at 5mg/day, until undesirable side effects, or maximum positive response achieved. Average dose: 10-20 mg/day.

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/	Number withdrawn/ lost to fu/
PCT > 6 mos				
DEX				
Conrad 1971 (Poor)	NR NR NR	NR	1350/262/106/68	NR

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
PCT > 6 mos	
DEX	
Conrad 1971 (Poor)	**Mean difference scores between baseline and post-testing** reported as variable: grp A (placebo/no tutor); grp B (placebo/tutor); grp C (dextroamphetamine/no tutor); grp D (dextroamphetamine/tutor); (p-Value) Motor Coordination: -.17; 24; 18; .25; (.20) Repeating a Motor Pattern: .00; 1.00; .71; 1.50; (.02) Visual Tracking: .00; .59; .18; .31; (.12) Motor Activity: -.06; .18; .65; .69; (.01) Distractibility: .22; .35; .59; .44; (.50) Hyperkinetic Score: 2.28; 5.59; .9.29; 6.25; (.08) Behavior Rating By Teacher: 3.00; 2.77; 2.59; 2.19; (.001) Behavior Rating By Parent: 2.94; 2.77; 2.06; 1.94; (.001) Spatial Orientation: 1.33; 1.65; .71; 2.00; (.50) Koppitz Errors: 1.44; 2.18; 3.06; 4.25; (.07) Frostig I: -.56; -.18; .53; -.25; (.30); Frostig II: -.39; -.18; 1.00; .00; (.12) Frostig III: .06; 1.29; 1.47; 1.69; (.25); Frostig IV: -.56; -.47; 1.18; .31; (.02) Frostig V: -.39; .53; 1.00; .69; (.02); Frostig PQ: -4.61; 2.18; 10.41; .69; (.02) Frostig Stars: .56; .53; .88; .56; (.50) WISC Subtests Information: -1.17; .88; -.06; 1.06; (.005); Comprehension: -.33; .06; -.29; 1.00; (>.50) Arithmetic: .28; .59; .47; -.31; (>.50); Similarities: .72; -.24; .82; -.06; (>.50) Digit Span: 1.39; .77; 2.18; 1.69; (>.50); Picture Completion: .02; -.06; .71; .06; (>.50) Picture Arrangement: .89; 1.41; .41; 1.75; (>.50); Block Design: -.50; 1.29; -.06; .56; (>.50) Object Assembly: .67; .88; 1.06; 2.75; (.17); Coding: .72; .82; 3.35; 2.00; (.07) WISC Verbal IQ: .89; 2.18; 4.53; 3.94; (>.50) WISC Performance Scale: 2.94; 6.06; 6.88; 9.19; (.30) WISC Full-Scale IQ: 2.11; 4.41; 6.24; 7.43; (.12) Temporal Order: 1.44; 2.00; 1.53; 2.19; (>.50) Bender Recall: .80; .93; 1.00; 1.38; (>.50) WRAT Reading: 6.33; 5.59; 5.29; 4.94; (>.50) WRAT Arithmetic: 3.06; 3.47; 5.41; 4.44; (.18)

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects	Adverse effects reported	Total withdrawals; withdrawals
PCT > 6 mos			
DEX			
Conrad 1971 (Poor)	NR	NR	NR

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
MPH			
Ialongo 1993 Fair	Children had to meet DSM-III-R criteria for ADHD, based on a) Conners Parent and Teacher Hylerkinesis Indices scores >=2 SD's above published means; b) a clinical interview with the parents; and c) the results of psychometric testing. A pediatrician and psychiatrist had to both agree with ADHD diagnosis in their review of available data. Children with a comorbid anxiety and/or depressive disorder and with gross physical impairments, intellectual deficits, and psychosis in either child or parent(s) were excluded.	Original study of n=107: Conduct disorder: 7.5% (n=8) Oppositional defiant disorder: 43.0% (n=46)	All MPH and behavioral treatments had been discontinued 9 months prior to follow-up. In short-term portion of study, children were randomly assigned to: placebo alone; low-dose MPH=0.4 mg/kg/day; high dose MPH=0.8 mg/kg/day; placebo + behavioral parent training (PT) and child self-control instruction (SC); low-dose MPH+PT+SC; high dose MPH+PT+SC

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/	Number withdrawn/ lost to fu/
MPH				
Ialongo 1993 Fair	Average Age = 8.27 years Male = 77.4% White = 84.9% African-American = 9.4% Hispanic = 3.8% Asian American = 1.9%	NR	117/107/96	18/7/71 analyzed

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
MPH	
Ialongo 1993 Fair	Overall trend (the exception was the parent report data) towards an erosion of treatments gains seen across treatments. ("A table of means and standard deviations by condition and over time for each of the outcome measures is available from the senior author.") -Only significant contrast seen for PT+SC treatment effect for posttest to follow-up (fu) : F[5,56]=3.69, p=0.006. Univariate F for PT+SC treatment effect was significant for each of the parent report measures: CPRS, F[1,64]=14.31, p<0.001; SNAP, F[1,62]=4.89, p=0.031 CBCL total problems, F[1,61]=12.03, p=0.001; CBCL externalizing F[1,61]=11.07, p=0.001 CBCL aggression F[1,60]=6.29, p=0.015 -Medication alone condition: modest deterioration or no gain from posttest to fu; in contrast, children in PT+SC showed improvements from posttest to fu on Conners Hyperkinesis Index, SNAP total score, and CBCL (total problems, externalizing, and aggression) (no data given). -Multivariate Fs for pretest to posttest and postest to fu contrasts were significant for medication by period effect: pretest to posttest:F[4,120]=5.05, p=0.001; postest to fu: F[4,121]=3.37, p=0.012 Univariate Fs for off-task behavior: pretest to posttest:F[2,62]=10.36, p<0.001; postest to fu: F[2,60]=7.18, p=0.002 -Children receiving stimulant medication showed a significantly greater deteriorization in posttest to fu scores than did children receiving placebo. (explanation: the non-medicated children showed virtually no change pretest to posttest or posttest to fu, whereas medicated children did show significant imrovement from prettest to posttest and deterioration of those gains from posttest to fu.) (no data given) -No evidence of greater maintenance of treatment gains at fu were found with chidlren receiving PT+SC+medication. (no data given).

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects	Adverse effects reported	Total withdrawals; withdrawals
MPH			
Ialongo 1993 Fair	NR for follow-up group	NR for follow-up group AE details not specified for short-term group, though 3 withdrew because of them and 13 dropped out "owing to concerns about the medication, or insufficient time to attend the groups, or dissatisfaction with treatment efficiency".	18 withdrawals/3 withdrew to AE's during the short-term part of the trial; 7 lost to follow-up

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Kupietz 1987 Fair	Children between 7 and 13 includsive, with an IQ>=80, meeting DSM-III criteria for ADD with Hyperactivity (ADDH) and Developmental Reading Disorder, whose parents confirmed in an interview that hyperactivity had been present for >=2 years, a teacher rating of >=2.5 (on a 1 to 4 scale) on the Hyperactivity factor of the Conner's TRS. Children with an additional Axis I psychiatric diagnosis or uncorrected hearing or visual deficits were excluded.	Developmental Reading Disorder	0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg or placebo per day Duration was a total of 28 weeks: 14 weeks of treatment, 1 wk placebo, 12 wks treatment, 1 wk placebo

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/	Number withdrawn/ lost to fu/
Kupietz 1987 Fair	Mean age = 9.7 years Male = NR White = NR	**At baseline:** Conner's TRS mean Hyperactivity score = 3.08 Reading Grade Level = 4.5 (mid fourth-grade) FSIQ mean score = 93.8 VIQ mean score = 91.5 PIQ mean score= 97.8	NR/NR/58	11 withdrew before completing the 28-week drug protocol/NR/47, but sample size varies across dependent measures due to missing forms from parents or teachers

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
Kupietz 1987 Fair	Conners TRS scores with the adjusted means for Agressiveness (I), Inattentiveness (II), and Hyperactivity (IV) Factors analyzed together: Mean ratings for dosage (all weeks combined): placebo, 0.3mg, 0.5mg, 0.7mg, and 0.7mg: 2.43, 1.93, 1.85, 1.62* *_Post-hoc analysis_ : 0.7 mg/kg group received significantly lower ratings than placebo (p=NR) Mean ratings for week (all dosages combined): week 2, week 14, week 27: 1.96, 1.89, 2.05* *_Post-hoc analysis_ : Means for Week 14 compared to Week 2 was considered unchanged (p-value NR); but the increase between Week 14 and Week 27 was considered significant (p-value NR). DESB Scale: adjusted mean ratings for placebo, 0.3 mg, 0.5 mg, 0.7mg (all weeks combined): 140.3, 128.0, 112.6, 104.9 *_Post-hoc Analysis:_ only 0.7mg and placebo roups were found to differ significantly (p-value NR) Conners ARS scores, Combined Adjusted Mean ratings for dosage (all weeks combined): placebo, 0.3mg, 0.5mg, 0.7mg, and 0.7mg: 2.51, 2.39, 2.36, 1.80 *_Post-hoc analysis_ : 0.7 mg were rated significantly less hyperactive than placebo (p=NR) DCB Scale: Mean parent ratings for weeks 2, 14, 27 (all dose groups combined): 185.6, 180.0, 132.2* *_Post hoc analysis_ : Week 27 results were significantly lower than Week 2 or 14 results. At each study week, 0.7mg were lowest; only at week 14 was 0.7mg significantly lower than placebo or 0.3mg (p-value NR) WWPAS: No dose group effects were obtained; the main effect for weeks only approached significance as a main effect (p=0.058). Mean activity ratings for weks 2, 14, 27 (all dosages combined) were 18.5, 16.5, 16.4 Paired-Associate Learning (PAL): Neither dose group nor study week was significant, but there was a significant interaction between these variables (F=3.34, p<0.05). Adjusted error scores show a tendency for errors to decrease as a function of MP dosage across the 0.5mg and 0.7mg groups (p-value NR). _Post-hoc analysis_ : at Week 27, 0.7mg group made significantly fewer errors than placebo or 0.3mg (p-value NR). STM Task: no drug effects were obtained on latency of correct response measure; thus, these data not reported. A main effect of matrix (F=51.51, p<0.001) and a significant interaction between dose group and study week (F=3.68, p<0.02). *_Post-hoc analysis:_ significantly more correct responses were made to matrix size 3 than to 9 or 15 (p-value NR); at week 2 the 0.7mg group made significantly more correct responses than placebo, but not at week 27 (p-values NR).

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects	Adverse effects reported	Total withdrawals; withdrawals
Kupietz 1987 Fair	NR	NR	11 withdrawals; study states that some withdrew due to side effects, but does not give a specific number

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
ADHD Drug Versus Non-			
MTA Cooperative Group 1999. 2004	Children between 7 and 9.9 years (grades 1-4), in residence with same primary caretaker >=last 6 months, who met the DSM-IV criteria for ADHD Combined Type, using the Diagnostic Interview Schedule for Children (DISC) parent report version 3.0, supplemented with up to 2 symptoms identified by children's teachers for cases falling just below DISC threshold. Exlucsion criteria: situations that would prevent families' full participation in assessmests or treatment, or that might require additional treatment incompatible with study treatments (ex. child currently in hospital, child currently in another study, child with =<80 on all WISC-III scales and SIB, bipolar disorder, psychosis, or personality disorder, chronic serious tics or Tourette syndrome, OCD serious enough to require separate treatment, neuroleptic medication in previous 6 months, major neurological or medical illness, history of intolerance to MTA medications, ongoing or previously unreported abuse, parental stimulant abuse in previous 2 years, same classroom as child already in MTA study, non-English-spea	ODD: 39.9% (n=231) Conduct Disorder: 14.3% (n=83) Anxiety Disorder: 33.5% (n=194) Tic Disorder: 10.9% (n=63) Affective Disorder: 3.8% (n=22) Mania/hypomania: 2.2% (n=13)	4 different arms of treatment: medication management [MM] only (n=144), behavioral treatments [BT] (no medication) (n=144), combined medication and behavioral treatment [CT] (n=145), and standard community care [CC] (in which community doctors decided the best mode of treatment for their individual patients) (n=146). -Blinded physicians agreed on best dose of medication for subjects in both the MM and CT groups after a 28-day titration (the only DB part of study) - at which point blind was broken and this agreed-on dose became the subject's initial maiantenatnce dose. -MM and CT subjects originally given MPH: 77.3% (n=198 of 256 who completed titration) MM and CT subjects originally given dex: 10.2 % (n=26) MM and CT subjects originally given no medication: 12.5% (n=32) average initial dose of MPH = 30.5 mg/day -At the end of 14 months, MM and CT subjects taking MPH: 73.4% (n=212 of 289 completing both MM and CT) MM and CT subjects taking dex: 10.4% (n=30) MM and CT subjects on other drugs: 3.1% (n=9) MM and CT subjects on no medication: 13.1% (n=38) CT subjects received 31.2 mg of MPH versus MM=37.7 mg of MPH by tre -At the end of 14 months, CC subjects taking MPH: 57.5% (n=84 of 146 CC subjects) CC subjects taking dex: not specified CC subjects on other drugs: 16.4% (n=24) CC subjects on no medication: not specified Mean total daily dose for CC subjects=22.6 mg of MPH at treatment end 14 Month Duration for all treatment arms

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/	Number withdrawn/ lost to fu/
ADHD Drug Versus Non-				
MTA Cooperative Group 1999. 2004	Mean Age = 8.5 (range: 8.4-8.6) years Male = 80.3% (n=465) White = 60.6% African American = 19.9% Hispanic = 8.3%	WISC-III IQ, mean score= 100.9 Conners Teacher Rating Scale, mean score = 1.32 Conners Parent Rating Scale, mean score = 0.83 Welfare recipients = 19.0% Subjects living with 2-parent family = 68.4%	4541/609/579	NR/NR/526 analyzed (number gotten from test score subject numbers at 14 months)

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
ADHD Drug Versus Non-	
MTA Cooperative Group 1999. 2004	For all results, significance is taken after Bonferroni-corrected p-values 1) **ADHD symptoms** a) Inattention rated by teacher: MM>BT (p=0.001); CT vs.MM (p=ns); CT>BT (p=0.005); CT>CC (p=0.001); MM>CC (p=0.001); BT vs.CC (p=ns) b) Inattention rated by parent: MM>BT (p=0.001); CT vs.MM (p=ns); CT>BT (p=0.001); CT>CC (p=0.001); MM>CC (p=0.001); BT vs.CC (p=ns) c) Hyperactive-impulsive rated by teacher: MM vs.BT (p=ns); CT vs.MM (p=ns); CT vs.BT (p=ns); CT>CC (p=0.001); MM>CC (p=0.001); BT vs.CC (p=ns) d) Hyperactive-impulsive rated by parent: MM>BT (p=0.001); CT vs.MM (p=ns); CT>BT (p=0.001); CT>CC (p=0.001); MM>CC (p=0.001); BT vs.CC (p=ns) e) Classroom rated by classroom observer: MM vs.BT (p=ns); CT vs.MM (p=ns); CT vs.BT (p=ns); CT vs.CC (p=ns); MM vs.CC (p=ns); BT vs.CC (p=ns) 2) **Aggression-ODD** a) Rated by teacher: MM vs.BT (p=ns); CT vs.MM (p=ns); CT vs.BT (p=ns); CT>CC (p=0.004); MM>CC (p=0.004); BT vs.CC (p=ns) b) Rated by parent: MM vs.BT (p=ns); CT vs.MM (p=ns); CT>BT (p=0.001); CT>CC (p=0.002); MM vs.CC (p=ns); BT vs.CC (p=ns) c) Rated by classroom observer: MM vs.BT; CT vs.MM; CT vs.BT; CT vs.CC; MM vs.CC; BT vs.CC (p=ns for all 6 comparisons) 3) **Internalizing symptoms- SSRS Internalizing rated** a) by teacher: MM vs.BT; CT vs.MM; CT vs.BT; CT vs.CC; MM vs.CC; BT vs.CC (p=ns for all 6 comparisons) b) by parent: MM vs.BT (p=ns); CT vs. MM (p=ns); CT>BT(p=0.001); CT>CC (p=0.001); MM vs.CC (p=ns); BT vs. CC (p=ns) c) MASC rated by child: MM vs.BT; CT vs.MM; CT vs.BT; CT vs.CC; MM vs.CC; BT vs.CC (p=ns for all 6 comparisons) 4) **Social Skills- SSRS rated** a) by teacher: MM vs.BT; CT vs.MM; CT vs.BT (p=ns for all three); CT>CC (p=0.001); MM almost equivalent to CC (p=0.009); BT vs.CC (p=ns) b) by parent: MM vs.BT; CT vs.MM; CT vs.BT; CT vs.CC; MM vs.CC; BT vs.CC (p=ns for all 6 comparisons) 5) **Parent-child relations** a) Power assertion rated by parent: MM vs.BT; CT vs.MM; CT vs.BT (p=ns for all three); CT>CC (p=0.003); MM vs.CC (p=ns); BT almost equivalent to CC (p=0.005) b) Personal closeness rated by parent: MM vs.BT; CT vs.MM; CT vs.BT; CT vs.CC; MM vs.CC; BT vs.CC (p=ns for all 6 comparisons) 6) **Academic acheivement** a) Reading: CT>BT and CT>CC in pairwise comparisons (p=0.001) b) Mathematics: no significant main effects for treatment group, so no pairwise comparisons were performed c) Spelling: no significant main effects for treatment group, so no pairwise comparisons were performed 24-Month Outcomes: CT vs MM vs BT vs CC 1) Medication use (%)- 14-24 months: 86 vs 85 vs 44 vs 69, p<0.001; 24 month: 70 vs 72 vs 38 vs 62 2) Mean dosage (mg/day): 30.4 vs 37.5 vs 25.7 vs 24, p<0.0001 3) the adventage of CT/MM over BT/CC remained significant (p=0.002) for ADHD symptoms and almost signigicant (p=0.016) for ODDsumptoms 4) The proportion of children with SNAP item means ≤ (near normalization or "excellent responders") at 24 months: 48 vs 37 vs 32 vs 28

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects	Adverse effects reported	Total withdrawals; withdrawals
ADHD Drug Versus Non-			
MTA Cooperative Group 1999. 2004	Side-effects were monitored monthly using parent-completed 13-item Pittsburgh Side Effects Rating Scale (ratings=not present, mild, moderate, severe)	245 combined treatment/medication families reported side effects: No side-effects: 88 (35.9%) Mild side effects: 122 (49.8%) Moderate side effects: 28 (11.4%) Severe side effects: 7 (2.9%) (6 of 11 reported servere side effects (depression, worrying, or irritability) could have been due to non-medication factors)	20 complete droupouts by 14 months = 3.5%; Withdrawals due to AE's: not specified

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
MPH vs.parent training			
Firestone 1986	Children aged 5-9 years, with DSM-III diagnosis of ADHD, and with rating of 1.5 or higher on Teacher's Activity Index.	NR	Subjects randomly assigned to one of three grps: parent trg and meds (PTMEDS), parent trg and placebo (PTPL) or meds only (MED). Doses: raised or lowered by % mg steps, based on reports of symptoms, until individual optimal dosages were established (decrease in problmenatic behavior and absence of negative side effects), average dose was 22 mg/day. Duration: 24 months. Dosing schedule NR.

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/	Number withdrawn/ lost to fu/
MPH vs.parent training				
Firestone 1986	ages: 5-9 yrs gender: NR ethnicity: NR	NR	NR/NR/73	NR/ 21 lost to fu/ 52 analyzed for entire 2 yr period

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
MPH vs.parent training	
Firestone 1986	**Test scores at 3 mos: (mean scores; SD; n)** Hyperactivity Index: MED: .81; .44; (n=11); PTPL: 1.12; .56; (n=9); PTMED: 1.03; .46; (n=10) Conduct Problems: MED: 6.45; 4.42; (n=11); PTPL: 6.89; 4.23; (n=9); PTMED: 5.8; 2.81; (n=10) Reaction Time: MED: .64; .19; (n=12); PTPL: .75; .22; (n=8); PTMED: 5.8; 2.81; (n=10) Verbal Grade: MED: 3.42; 1.54; (n=10); PTPL: 2.51; 1.62; (n=8); PTMED: 3.36; 1.22; (n=9) **Test Scores at 10-12 mos: (mean scores; SD; n)** Hyperactivity Index: MED: .96; .59; (n=11); PTPL: 1.07; .55; (n=9); PTMED: .92; .36; (n=10) Conduct Problems: MED: 5.91; 3.61; (n=11); PTPL: 6.44; 4.02; (n=9); PTMED: .92; .36; (n=10) Reaction Time: MED: .59; .13; (n=12); PTPL: .70; .15; (n=8); PTMED: .63; .25; (n=10) Verbal Grade: MED: 3.56; 1.62; (n=10); PTPL: 3.23; 2.16; (n=8); PTMED: 3.97; 1.34; (n=9) **Test Scores at 22-24 mos: (mean scores; SD; n)** Hyperactivity Index: MED:1.09; .60; (n=11); PTPL: 1.09; .63; (n=9); PTMED: 1.06; .59; (n=10) Conduct Problem: MED: 6.97; 4.41; (n=11); PTPL: 4.51; 3.57; (n=9); PTMED: 1.06; .59; (n=10) Reaction Time: MED: .60; .11; (n=12); PTPL: .64; .14; (n=8); PTMED: .52; .12; (n=10) Verbal Grade: MED: 4.56; 1.70; (n=10); PTPL: 4.29; 2.74; (n=8); PTMED: 5.14; 1.92; (n=9)

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects	Adverse effects reported	Total withdrawals; withdrawals
MPH vs.parent training			
Firestone 1986	report of symptoms from teachers.	NR	NR

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Brown 1985	40 boys whose parents and teachers agreed that he demonstrated, in serious and persistent form (symptoms demostrated from infancy or early childhood for a duration of >=12 months prior to referral), symptoms associated with ADHD. Parent and teacher interviews were conducted to ascertain the child's symptoms and emotional climate in the home after health care or special education personnel referred the boy to the study. Each boy also demonstrated a reading deficit of at least two grade levels. Excluded were boys with symptoms that seemed to stem from stress at home or from inconsistent child management practices; with major diseases; with obvious physical defects; with gross neurological, sensory, or motor impairment; or with psychosis.	Reading deficits	MPH Doses were 0.3 mg/kg - twice daily: in the morning and at lunch Individual doses ranged from 5 to 15 mg/day Cognitive training: individual twice-weekly one hour sessions over a total of 12 weeks (24 session total/individual). Modeling, self-verbalization, and strategy training were taught. Mothers observed several training sessions with another trainer from behind a one-way mirror and were instructed on how these procedures could be applied at home. There were four treatment groups: no treatment (n=10); MPH only (N=10); Cognitive Training only (n=10) [CTO]; and Combined Cognitive Training and MPH treatment (n=10) [Combined] Cognitive training lasted 12 weeks; MPH continued for the "duration of study"
Atomoxetine Newcorn 2006			

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/	Number withdrawn/ lost to fu/
Brown 1985	Mean age = 11.36 years Male = 100% Ethnicity NR	Mean IQ score (obtained from WISC-R): 101.92 (range: 91-136) Mean ACRS score: 18.55 (range: 17-22) Separate ANOVAs for these variables show that none of the four groups differed in age, IQ, or ACRS (no data given) Since 10 boys were non-random, a one-way multiple ANOVA was performed on pre-treatment scores; result was nonsignificant F ratio, F(3,36)=0.47, n.s.; these results indicate equality prior to treatment between subgroups.	NR/NR/40	NR/NR/40
Atomoxetine Newcorn 2006				

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
Brown 1985	F ratios determined using separate MANOVAs to determine differences in the effectiveness of treatment and to determine the persistence of each tre delayed posttesting (DPT): MPH only; Combined; CTO; No Treatment: F(2,34)=3.95, p<0.001; F(2,34)=5.06, p<0.0001; F(2,34)=1.88, p<0.69; F(2,34)=0.53, p<0.95 **Comparisons of Univariate Measures by Condition** *p-values* for: MPH only; Combined Therapy; Cognitive Training only (CTO); and No Treatment* CCT Omissions: p<0.0001; p<0.0001; p<0.07 (as); ns CCT Comissions: ns; p<0.08 (as); ns; ns MFFT Error: p<0.0001; p<0.008; p<0.08 (as); ns MFFT Latency: ns; p<0.00001; p<0.001; p<0.01 CEFT Total correct: p<0.01; ns; p<0.005; ns WISC-R Attention factor: p<0.004; p<0.06; p<0.03; ns WRAT Arithmetic: p=ns for all four subgroups WRAT Reading: p=ns for all four subgroups Durrell Listening Comprehension: p<0.005; p<0.006; p<0.03; ns Detroit Subtests (3): p=ns for all four subgroups on all 3 subtests Conners Teacher: p<0.0001; p<0.004; ns; ns Conners Parent: p<0.05; p<0.002; ns; ns Teacher Rating Attention: p<0.005; p<0.05: ns; ns Teacher Rating Impulsivity: p<0.02;p<0.02; p<0.07 (as); ns Self-rating Impulsivity: p<0.0001; p<0.0001; ns; ns *p-values: significance when p<0.05; not significant = ns, approached significance=as [value given] Duncan's Multiple Range Test post-hoc analyses were performed by condition for each of the significant univariate dependent measures. Differences between pretest and posttest (p<0.05) and pretest and DPT (p<0.05) were signficant, but differences between posttest and DPT were ns (no p-value given). Canonical correlation coefficients (Rc2) for the multivariate analyses for MPH Only; Combined; CTO 0.963; 0.971; 0.926 (amount of variance in dependent measures across pre-, post-, and DPT accounted for by the differences in MPH only and Combined treatments was virtually the same).
Atomoxetine Newcorn 2006	

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects	Adverse effects reported	Total withdrawals; withdrawals
Brown 1985	NR	NR	NR
Atomoxetine Newcorn 2006			

Evidence Table 8. Quality in long-term efficacy trials

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?	Reporting of attrition, crossovers, adherence, and contamination
Conrad 1971	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Brown 1985	NR	NR	NR	Yes	NR	No	No	NR, NR, NR, NR
Kupietz 1987	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR
Ialongo 1993	NR	NR	No, more non-white children in placebo group	Yes	Yes	Yes	Yes	Yes, NR, NR, NR

Evidence Table 8. Quality in long-term efficacy trials

Author, Year Country	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating	*External Validity* Number screened/eligible/ enrolled	Exclusion criteria
Conrad 1971	No/No	No	NR	Poor	NR/96/96	NR
Brown 1985	NR	NR	NR	Poor	NR/NR/40	Gross nerological, sensory, or motor impairment or psychosis
Kupietz 1987	No/No	No, sample size varied across dependent measures, based on incomplete data	No	Fair	NR/NR/58	Additional Axis I psychiatric diagnosis or uncorrected hearing or visual deficits
Ialongo 1993	No/No	Yes	No	Fair	117/107/96	Comorbid anxiety and/or depressive disorder; gross physical impairments, intellectual deficits or psychosis

Evidence Table 8. Quality in long-term efficacy trials

Author, Year Country	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Conrad 1971	NR/NR	NR	Yes	NY State Department of Mental Hygiene Contract No. C36725	
Brown 1985	NR/NR	NR	Yes	NR	
Kupietz 1987	NR/NR	NR	Yes	NIMH grant MH 36004	
Ialongo 1993	NR/NR	NR	Yes	NR	

Evidence Table 8. Quality in long-term efficacy trials

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?	Reporting of attrition, crossovers, adherence, and contamination
MTA	NR	Yes	No, significant differences across treatment groups in age	Yes	Yes	No	No	Yes, Yes, Yes, Yes
Firestone 1986	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR

Evidence Table 8. Quality in long-term efficacy trials

					External Validity	
Author, Year Country	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**
MTA	NR	No	No	Fair	4541/609/579	ex. child currently in hospital, child currently in another study, child with =<80 on all WISC-III scales and SIB, bipolar disorder, psychosis, or personality disorder, chronic serious tics or Tourette syndrome, OCD serious enough to require separate treatment, neuroleptic medication in previous 6 months, major neurological or medical illness, history of intolerance to MTA medications, ongoing or previously unreported abuse, parental stimulant abuse in previous 2 years, same classroom as child already in MTA study, non-English-speaking primary caretaker, no telelphone, suicidal or homicidal, another child in same household in MTA study
Firestone 1986	NR	No	No	Fair	NR/NR/73	Definite signs of brain damage, epilepsy, or psychosis

Evidence Table 8. Quality in long-term efficacy trials

Author, Year Country	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
MTA	NR/NR	No	Yes	NIMH grants	
Firestone 1986	NR/NR	NR	Yes	Ontario Ministry of Health grants	

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout Period
Bupropion SR vs methylphenidate				
Kuperman, 2001 U.S. (Fair)	DB RCT parallel groups	Patients were recruited from the community through newspaper ads. Subjects were required to meet DSM-IV criteria for ADHD at time of study, have a chronic course of ADHD symptoms from childhood to adulthood, and have moderate or severe impairment due to ADHD symptoms.	Methylphenidate was titrated over 1 week to a maximum dose of 0.9 mg/kg/day, administered at 8AM, noon, and 4 PM. Bupropion SR was titrated over 2 weeks to a maximum of 300 mg/day as follows: 200 mg at 8AM and 100 mg at 4PM, with placebo taken at noon. Placebo tid: 8AM, noon, 4 PM. Duration 7 weeks	7-day placebo lead-in; Washout NR

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Bupropion SR vs methylphenidate			
Kuperman, 2001 U.S. (Fair)	NR	CGI Severity; CGI Improvement, with response defined as a score of 1 (very much improved) or 2 (much improved) ADHDRS-self; HAM-D, HAM-A; Neuropsychological assessments: HVLT, Digit Ordering Test, Trails A & B; Verbal Fluency; Conners' CPT	Mean age 32.4 70% male Ethnicity NR

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Bupropion SR vs methylphenidate			
Kuperman, 2001 U.S. (Fair)	Mean years of education: 15.2	NR/NR/37 N enrolled in each group not reported	7 (18.9%) withdrew, 5 before and 2 after randomization; 0 lost to fu; 30 (81%) analyzed: bupropion n=11 methylphenidate n=8 placebo n=11

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Results
Bupropion SR vs methylphenidate	
Kuperman, 2001 U.S. (Fair)	Bupropion vs methylphenidate vs placebo, mean change in score: ADHDRS-self -13.7 vs -10.1 vs -12.4 (ns) HAM-D -1.5 vs -0.1 vs -2.9 (ns); HAM-A -3.6 vs -3.3 vs -3.1 (ns) % CGI responders 64% vs 50% vs 27% (ns for comparison between drug and placebo) Neuropsychological assessment, mean change in score: HVLT immediate recall +3.5 vs +2.0 vs -0.2 (ns) HVLT delayed % 0.0 vs 0.0 vs -0.1 (ns) Cooper digit ordering +7.2 vs +4.5 vs +3.5 (ns) Trails A -5.4 vs -2.1 vs -8.1 (ns) Trails B -5.0 vs -9.5 vs -9.8 (ns) Verbal fluency +6.5 vs +7.1 vs +1.1 (ns) CPT attentiveness +0.1 vs +0.8 vs +0.2 (ns)

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals by treatment; withdrawals due to adverse events
Bupropion SR vs methylphenidate			
Kuperman, 2001 U.S. (Fair)	Elicited by investigator	Insomnia: 15.4% in bupropion, 16.7% in methylphenidate Also in bupropion: dry mouth 30.7%, 15.4% headache, 15.4% insomnia Also in methylphenidate: 25% appetite suppression, 16.7% tremor, 16.7% sweating, 16.7% jitteriness For placebo: 16.7% tiredness	Withdrawals by treatment group unknown; Due to AEs: 2 in methylphenidate 1 in placebo

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Comments
Bupropion SR vs methylphenidate	
Kuperman, 2001 U.S. (Fair)	

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout Period
Levin 2006	DB RCT	Meet DSM-IV criteria for opiate dependence and adult ADHD, between the age of 18 and 60, and on the same dose of methadone for at least 3 weeks.	Sustained-release MPH, sustained-release BPR and placebo. Duration 12 weeks and included a 2-week placebo lead-in phase, a 2-week dose titration period followed by 8 weeks at a stable dose.	2 week placebo lead-in phase

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Levin 2006	Cocaine All were taking methadone	Adult ADHD rating scale (AARS) and CGI; Response was a reduction in scales by 30%; Assessed weekly	Placebo/ MPH/ Bupropion Mean age 39/40/38 Male (%) 55/59/66 Ethnicity (%) White 39/37/42 Black 21/22/18 Hispanic 39/41/39

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Levin 2006	Placebo/ MPH/ Bupropion Mean years of education: 12/12/12 Currently employed (%): 43/58/89	526/215/98	Placebo/ MPH/ Bupropion Withdrawals 8/11/10 Analyzed 25/32/33

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Results
Levin 2006	Placebo/ MPH/ Bupropion AARS response 46% (15) / 34% (11) / 49% (16) P = 0.482 CGI response 39% (13) / 19% (6) / 30% (10) P = 0.192 AARS + CGI 21% (7) / 9% (3) / 15% (5) P = 0.422

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals by treatment; withdrawals due to adverse events
Levin 2006	NR but rated 0-3 (none-severe)	Fatigue Placebo 9% Increased sweating MPH 6% Bupropion 9%	Placebo/ MPH/ Bupropion Withdrawals 8/11/10 Due to Aes 2/1/0

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Comments
Levin 2006	

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout Period
Dextroamphetamine vs guanfacine				
Taylor, 2001 U.S. (Fair)	DB RCT, crossover study	Subjects were outpatient adults with ADHD (met DSM-IV criteria), with corroborating childhood history from at least one relative and examples of schoolwork and prior psychologic testing, scoring above 93rd percentile of symptom severity on both the childhood and adult versions of the ADHD Behavior Checklist.	Daily dosing was qd on awakening, beginning with 1 capsule (containing either lactose, 0.05 mg guanfacine, or 2.5 mg DAMP) and increased by an additional capsule every day to 2 days as tolerated. DAMP maximum 20 mg/day, mean 10.2 mg/day Guanfacine maximum 2.0 mg/day, mean 1.10 mg/day Placebo 2-week treatment phases of placebo, guanfacine, and dextroamphetamine (DAMP) were separated by 4-day washouts	Run-in NR; 4-day washouts between treatments

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Dextroamphetamine vs guanfacine			
Taylor, 2001 U.S. (Fair)	NR	Five self-administered rating scales at baseline and on the last day of each treatment phase within 4 hrs of last dose: 2 scales for ADHD (DSM-IV ADHD behavior checklist for adults, and CSCA, and one scale each for depression, anxiety, and OCD: BDI, Ham-A, Y-BOCS. Patients also self-assessed task motivation, and how long medication effects lasted. Cognition tests: Stroop Color-World Interference Test, and CFL version of COWAT.	Mean age 41.2 41% male Ethnicity NR

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Dextroamphetamine vs guanfacine			
Taylor, 2001 U.S. (Fair)	100% completed high school; 23% completed college; 12% completed postgraduate degrees 70% had family history of ADHD All patients had either hyperactive or mixed subtype.	NR/NR/17	No withdrawals; No loss to followup; 17 analyzed, all exposed to both DAMP & guanfacine

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Results
Dextroamphetamine vs guanfacine	
Taylor, 2001 U.S. (Fair)	DAMP vs guanfacine: Duration of action 5.4 vs. 6.9 hours (p=0.006) Increased task motivation reported by 16 vs. 0 patients (p<0.001) Means for study measures: DSM-IV ADHD symptom total 24.2 vs 8.2 (ns); hyperactivity 10.2 vs 9.5 (ns); inattentive 14.0 vs 12.8 (ns) Copeland 66.5 vs 68.4 (ns) Beck depression 12.4 vs 12.8 (ns) Hamilton rating scale for anxiety 12.8 vs 10.8 (ns) Y-BOCS obsessions 4.5 vs 4.4 (ns); compulsions 3.7 vs 2.3 (ns) Cognitive: COWAT 79.5 vs 72.8 (ns) Stroop: Color 49.1 vs 48.8 (ns); Word 50.6 vs 51.1 (ns); Color-Word 52.4 vs 51.8 (ns); Interference 51.3 vs 50.8 (ns) Drug preference: 12 chose DAMP (citing positive effect on motivation compared with guanfacine); 4 chose guanfacine; 1 chose placebo

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals by treatment; withdrawals due to adverse events
Dextroamphetamine vs guanfacine			
Taylor, 2001 U.S. (Fair)	At end of each treatment phase, subjects completed a rating scale for side effects	Muscle tension 5 (29.4%) on DAMP Fatigue 4 (23.5%) on guanfacine	0 withdrawals

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Comments
Dextroamphetamine vs guanfacine	
Taylor, 2001 U.S. (Fair)	Data from the first phase was not reported separately. Outcomes were presented as combined data from all phases for each drug. The authors examined the effect of sequence in the crossover design, and report that no effect or interactions were found.

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout Period
Dextroamphetamine vs modafinil				
Taylor, 2000 U.S. (Fair)	DB RCT, crossover study	Subjects were older than 21, and from a single local community. Subjects had to meet DSM-IV criteria for ADHD by age 7 as well as currently, with chronic course, with at least moderate impairment from the symptoms, and provide corroborating history from at least one parent or older sibling, with evidence from schoolwork or prior psychologic testing. Subjects were required to score above the 93rd percentile of symptom severity.	DAMP 10-49 mg/day in 5 mg capsules; mean dose 21.8 mg/day Modafinil 100-400 mg/day in 50 mg capsules; mean dose 206.8 mg/day Placebo (lactose) Daily dosing was on awakening and again 5 hours later. Titration occurred over 4-7 days, with fixed dose thereafter for another 7-10 days. 2-week treatment phases of placebo, modafinil, and DAMP, separated by 4-day washouts.	Run-in NR; 4-day washout between treatments

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Dextroamphetamine vs modafinil			
Taylor, 2000 U.S. (Fair)	NR	At baseline and on the last day of each treatment phase within 3 hours of the last dose: self-rated ADHD behavior checklist for adults; self-rated BDI; clinician-administered Ham-A. Clinician-administered cognitive tests: letters C, F, and L of the COWAT; Wechsler Adult Intelligence Scale-Revised; Stroop-Color-Word Interference Test	Mean age 40.8 59% male Ethnicity NR

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Dextroamphetamine vs modafinil			
Taylor, 2000 U.S. (Fair)	100% completed high school; 55% completed college 91% had family history of ADHD 73% had child or sibling with ADHD Comorbidities: 46% had at least 1 episode of depression 14% anxiety disorder and past history of alcohol dependence	29/22/22	1 withdrawn 0 lost to fu; 21 analyzed, all exposed to both DAMP & modafinil

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Results
Dextroamphetamine vs modafinil	
Taylor, 2000 U.S. (Fair)	Cognitive mean scores, DAMP vs modafinil: COWAT Test 86.5 vs 87.7 (ns) Digit Span forward 10.3 vs 10.3 (ns); backward 7.6 vs 7.5 (ns) Stroop Color 50.2 vs 48.0 (ns); Word 48.8 vs 48.8 (ns); Color-Word 52.0 vs 51.6 (ns) DSM-IV ADHD behavior checklist mean scores, DAMP vs modafinil: Total 20.0 vs 18.3 (ns); Hyperactivity subscore 9.0 vs 7.3 (ns); Inattention subscore 11.0 vs 10.5 (ns) Drug preference: 48% chose DAMP, 43% chose modafinil, 10% chose placebo

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals by treatment; withdrawals due to adverse events
Dextroamphetamine vs modafinil			
Taylor, 2000 U.S. (Fair)	Side effect checklist, elicited by investigator on the last visit of each drug trial	DAMP vs modafinil: Insomnia 38 vs 19% (ns) Irritability 14 vs 19% (ns) Muscle tension 24 vs 19% (ns) Appetite suppression 24 vs 19% (ns) Anxiety 19 vs 10% (ns) Headaches 10 vs 10% (ns) Dizziness 10 vs 0% (ns) Lingual dyskinesia 5 vs 10% (ns)	1 withdrew before receiving treatment; No withdrawals due to AEs

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Comments
Dextroamphetamine vs modafinil	
Taylor, 2000 U.S. (Fair)	The report provides outcomes that are the averaged data collected at baseline and at the end of each treatment phase. Data from the first phase was not made separately available.

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout Period
Dextroamphetamine vs methyphenidate				
Matochik, 1994 U.S. (Fair)	DB, RCT	Subjects had to be adults who met following: 1) DSM-II criteria for ADHD 2) Utah criteria for attention deficit disorder in adulthood 3) a childhood history of ADHD 4) no history of an other maor psychiatric disorders.	DAMP 5 mg/day, up to 5-15 mg/day OR methylphenidate 5 mg/day, up to 5-25 mg/day. Duration: 6-15 weeks	1 month washout before starting meds

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Dextroamphetamine vs methyphenidate			
Matochik, 1994 U.S. (Fair)	NR	PET scan, (schedule NR) "How I Feel" Questionnaire administered on PET scan days Subject's Treatment Emergent Symptom Scale (schedule NR) modified Conner's Parent Rating Scale for Spouse/Close friend to complete (schedule NR) NIMH Clinical Global Impressions scale administered at tend of study period.	mean age 35.5 y 21 males, 16 females Ethnicity NR

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed
Dextroamphetamine vs methyphenidate			
Matochik, 1994 U.S. (Fair)	**Characteristic: methylphenidate vs d-amphetamine** had parents with attention-deficit disorder, residual type: 11/19 vs 12/18 had children with ADHD: 10/19 vs 10/18 WAIS IQ mean score: 108 vs 107 Wide Range Achievement Test scores Reading: 106.1 vs 102.7 Spelling: 105.6 vs 101.9 Arithmetic: 100.1 vs 97.2 Years of education: 15.4 vs 15.5 Socioeconomic status: 61.2 vs 56.6	NR/NR/37	NR/NR/ 37 analyzed: methyphenidate: n=19 DAMP: n=18

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Results
Dextroamphetamine vs methyphenidate	
Matochik, 1994 U.S. (Fair)	**Behavioral Effects of methyphenidate vs d-amphetamine** measure; Mean score at end of drug treatment (methyphenidate); p-Value vs d-amphetamine; p-Value Conner's rating scale Self: 5.0; 0.0001 vs 4.6; 0.0001 Spouse/Other: 5.7; 0.0001 vs 8.3; 0.0001 "How I Feel" Questionnaire Feel cranky or tired: 0.5; 0.02 vs NR; NR Have trouble keeping my mind on things: 0.5; 0.0001 vs 0.6; 0.0001 Feel like something bad might happen: 0.1; 0.008 vs NR; NR Feel restless, like moving around: 0.8; 0.0002 vs NR; NR Feel things may get messed up today: 0.0; NR vs NR; NR Feel I'm not much good at things: 0.3; 0.007 vs 0.2; 0.05 Feel sad: NR;NR vs 2.2; 0.008 Feel like I don't want to play with anyone: NR; NR vs 0.1; 0.01 Feel in a good mood: NR; NR vs 2.2; 0.008 Feel like my thoughts are going fast: NR; NR vs 0.2; 0.05 Feel tired and slow: NR; NR vs 0.0; NR Subject's Treatment Emergent Symptom Scale Trouble with sitting still: 0.7; 0.0001 vs 0.7; 0.002 Feeling sleepy: 0.4; 0.007 vs 0.2; 0.05 Not being happy: 0.3; 0.02 vs NR;NR Trouble with paying attention: 0.4; 0.0001 vs 0.6; 0.0001 Colds or sniffles: NR;NR vs 0.1; 0.01 Headaches: NR;NR vs 0.2; 0.03 Tiredness: NR;NR vs 0.3; 0.03 Trouble getting or staying asleep: NR;NR vs 0.3; 0.04 Getting along with parents: NR;NR vs 04; 0.007

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse effects reported	Total withdrawals by treatment; withdrawals due to adverse events
Dextroamphetamine vs methyphenidate			
Matochik, 1994 U.S. (Fair)	NR	1 subject reported adverse events (not specified) within first 2 weeks, and was immedately switched to other drug	None

Evidence Table 9. Head- to-head trials in adults with ADHD

Author Year Country Trial Name (Quality Score)	Comments
Dextroamphetamine vs methyphenidate	
Matochik, 1994 U.S. (Fair)	

Evidence Table 10. Quality assessment of head-to-head trials in adults with ADHD

	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?**
Bupropion SR vs methylphenidate							
Kuperman, 2001 U.S.	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported	Yes
Dextroamphetamine vs guanfacine							
Taylor, 2001 U.S.	Method not reported	Method not reported	Not reported	Yes	Yes but method not described	Not reported	Yes
Dextroamphetamine vs guanfacine							
Taylor, 2000 U.S.	Method not reported	Method not reported	Not reported	Yes	Yes but method not described	Not reported	Yes

Evidence Table 10. Quality assessment of head-to-head trials in adults with ADHD

	Internal Validity				
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**
Bupropion SR vs methylphenidate					
Kuperman, 2001 U.S.	Yes NR NR NR	No/ no	No: 81.1%	No	Fair
Dextroamphetamine vs guanfacine					
Taylor, 2001 U.S.	Yes NR NR NR	No/ no	Yes	No	Fair
Dextroamphetamine vs guanfacine					
Taylor, 2000 U.S.	Yes NR NR NR	No/ no	No: 95.4%	No	Fair

Evidence Table 10. Quality assessment of head-to-head trials in adults with ADHD

	External Validity	
Author, Year Country	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Bupropion SR vs methylphenidate		
Kuperman, 2001 U.S.	NR/NR/37	Patients were excluded if they had a clinically significant chronic medical condition, another current Axis 1 diagnosis, a history of tic disorders, mental retardation (IQ <80), organic brain disorders, clinically unstable psychiatric symptoms (suicidal behaviors, psychosis, violence, criminality), or substance abuse within 6 months; if taking other psychotropic medications. Any patient with a seizure history was excluded. Patients with eating disorders were excluded since they are predisposed to bupropion-induced seizures. Females of child-bearing potential were included only if using a medically approved form of contraception.
Dextroamphetamine vs guanfacine		
Taylor, 2001 U.S.	NR/NR/17	Excluded conditions already associated with frontostriatal pathology, including organic brain disorders, schizophrenia, and Tourette disorder; also excluded subjects with psychopathology possibly caused by neurologic insult. Also excluded medical conditions likely to affect mood or cognition, such as metabolic disorders, CNS conditions, mental retardation, untreated endocrine disorders, and pregnancy. Subjects using substances such as cannabis, amphetamines, cocaine, and heroin within 6 months of beginning drug trials were excluded. Subjects taking tricyclics, venlafaxine, or bupropion within 3 months, or stimulants within 2 weeks, before study were excluded.
Dextroamphetamine vs guanfacine		
Taylor, 2000 U.S.	29/22/22	Excluded narcolepsy and conditions associated with altered cognitive abilities including schizophrenia, Tourette's disorder, and diagnosable neurologic conditions; also excluded subjects with neurological soft signs that may be associated with frontal lobe cognitive deficits. Also excluded medical conditions likely to affect mood and condition, such as metabolic disorders, mental retardation, untreated endocrine disorders, and pregnancy. Also excluded the following: subjects using any cannabis, cocaine, heroin, or nonprescription amphetamines within 6 months of trial; subjects taking tricyclic antidepressants, venlafaxine, or bupropion within 3 months of trial; subjects taking prescription stimulants within 2 weeks prior to trial.

Evidence Table 10. Quality assessment of head-to-head trials in adults with ADHD

	External Validity				
Author, Year Country	**Run-in / Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Relevance**
Bupropion SR vs methylphenidate					
Kuperman, 2001 U.S.	Lead-in yes; Washout NR	No	Yes	Glaxo Wellcome	Yes
Dextroamphetamine vs guanfacine					
Taylor, 2001 U.S.	Run-in NR; 4-day washout between treatments	No	Yes	Not reported	Yes
Dextroamphetamine vs guanfacine					
Taylor, 2000 U.S.	Run-in NR; 4-day washout between treatments	No	Yes	Not reported	Yes

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Amphetamine mixture					
Spencer, 2001 U.S. (Fair)	DB RCT crossover design	Outpatient adults with ADHD aged 19-60, satisfying full diagnostic criteria for DSM-IV ADHD based on clinical assessment confirmed by structured diagnostic interview. ADHD diagnoses, with onset in childhood by age 7, chronic course until time of assessment, and associated with significant distress and disability.	Each medication was prescribed bid, taken at 7:30 AM and 2:30 PM. Amphetamine mixture (Adderall) was titrated up to 20 mg/day by week 1, 40 mg/day by week 2, and 60 mg/day by week 3. Mean dose at end of week 3 was 53.7 mg/day at end of week 3 (1st drug phase) Placebo mean dose 59.3 mg/day at end of week 3 Randomized crossover design with 1 week washout between treatment phases; Total trial duration 7 weeks	Run-in NR; 1-week blinded placebo washout between phases	Not reported (NR)
Atmoxetine					

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Amphetamine mixture				
Spencer, 2001 U.S. (Fair)	HAM-D, HAM-A, BDI before and after each arm of the study. CGI and ADHD rating scale administered weekly Neuropsychological test battery was administered 3 times, at baseline and after each study arm, and included an auditory version of the CPT, the Stroop test, and the Rey-Osterrieth Complex Figure. Improvement was defined as either a 30% reduction in the ADHD rating scale or "much" or "very much improved" on the CGI scale.	56% male Mean age 38.8 96% white	93% had at least 1 lifetime comorbid psychiatric disorder 67% had 1 or more first- or second-degree relatives with ADHD	103/41/30 Same subjects exposed to both treatments; N per drug in first treatment phase not reported.
Atmoxetine				

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results
Amphetamine mixture		
Spencer, 2001 U.S. (Fair)	3 (10%) withdrawals; 0% lost to fu; 27 (90%) analyzed. N per drug not reported	Mean change in ADHD rating scale during first treatment phase (Weeks 1-3), adderall vs placebo: -12 vs +1 (p<0.001) Mean change in score, data combined from 1st and 2nd drug phases, adderall vs placebo: Stroop Test: Word T-score +5.6 vs +4.0 ; Color T-score +5.0 vs +2.6; Color-Word T-score +1.4 vs +0.7; Interference T-score +1.2 vs +1.0 Rey-Osterrieth Complex Figure: copy organization -0.8 vs +0.1; copy accuracy +0.4 vs -0.1; delay organization +1.1 vs +1.5; delay accuracy +8.8 vs +9.5 CPT: number of hits +9 vs +7.8, number of omissions -7.9 vs -6.2; number late -1.39 vs -1.74 % of patients who improved, ie, >30% reduction on ADHD rating scale: 70.4% vs 7.4% % of patients who were "much" or "very much" improved on CGI scale: 66.7% vs 3.7%
Atmoxetine		Decrease in ADHD symptoms: tomoxetine: (11/21 subjects)-- week 2: p< 0.01; week 3: p<0.001 (3 week study) placebo: (2/10 subjects). Results from scales and tests at end of study reported as: paired tests of tomoxetine scores vs placebo scores; p-v

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Amphetamine mixture			
Spencer, 2001 U.S. (Fair)	Elicited by investigator; HAM-D, HAM-A, BDI	Adderall vs placebo: Insomnia 37 vs 14.8% (ns) Loss of appetite 29.6 vs 11.1% (p=0.03) Anxiety 25.9 vs 14.8% (ns) Headache 11.1 vs 7.41% (ns) Agitation 22.2 vs 7.4% (p=0.05)	Adderall vs placebo: Total withdrawals: 0 vs 3 (10%) Withdrawals due to AEs not reported
Atmoxetine			

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Amphetamine mixture	
Spencer, 2001 U.S. (Fair)	The mean ADHD rating scale score did not fully return to baseline after 1st phase of adderall and 1-week washout, but the order effect was not significant.
Atmoxetine	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Michelson, 2003/Reimherr 2005/Faraone 2005/Spencer 2006 31 outpatient sites in North America, country not otherwise specified (Fair)	2 identical, concurrent DB parallel group RCTs multi-site	Adults who met DSM-IV criteria for ADHD as assessed by clinical interview and confirmed by the Conners' Adult ADHD Diagnostic Interview were recruited from clinics and by advertisement. Patients were required to have at least moderate symptom severity, and the diagnosis had to be corroborated by a second reporter for either current symptoms (by a significant other) or childhood symptoms (by a parent or older sibling).	Atomoxetine mean dose 94.4 mg/day; administered in evenly divided doses in the morning and late afternoon/early evening, beginning at 60 mg/day. Patients with residual symptoms had dose increased to 90 mg/day after 2 weeks, and to 120 mg/day after 4 weeks. Placebo Duration 10-week	1-week washout, followed by 2-week placebo lead-in phase	NR
Wernicke, 2004 U.S. (Fair)	DB RCT parallel design with treatment and discontinuation phases	Adults who met DSM-IV criteria for ADHD as assessed by clinical interview and confirmed by the Conners' Adult ADHD Diagnostic Interview (CAAR-D) were randomized to acute treatment (approx. 10 weeks) with atomoxetine or placebo in 2 identical double-blind studies.	Atomoxetine vs placebo. For patients randomized to atomoxetine, dose was initiated at 60 mg/day (30 mg bid), titrated based on clinical response to a maximum of 120 mg/day (60 mg bid). After approximately 10 weeks, a 4-week double-blind discontinuation phase. Atomoxetine patients were randomized to either abrupt or tapered discontinuation, in which dose was reduced weekly.	NR/NR	NR
Spencer, 1998 U.S. (Fair)	DB, crossover design, parallel groups	Adults whom met full DSM-III criteria for ADHD by the age of 7 yrs, , with current, chronic symptoms, and endorsed impariment with the disorder.	Tomoxetine vs placebo. Patients randomized to Tomoxetine 40 mg/day in week 1, and 80 mg/day in weeks 2 and 3; or placebo.	Run-in NR/ 1 week of washout between the two 3 week periods.	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Michelson, 2003/Reimherr 2005/Faraone 2005/Spencer 2006 31 outpatient sites in North America, country not otherwise specified (Fair)	Self-rated version of CAARS and WRAADDS at baseline and endpoint; HAM-A and HAM-D; social and occupational functioning were assessed using the self-rated Sheehan Disability scale Primary outcome: sum of the Inattention and Hyperactivity/Impulsivity subscales of the investigator-rated CAARS	Mean age 40.2 63.6% male Ethnicity NR Mean age 42.1 66.4% male Ethnicity NR	Study I / Study II, ADHD subtype: Combined 71.8% / 60.5% Inattention 27.5% / 35.1% Hyperactive/Impulsive 0.7% / 4.3%	448/329/280 Atomoxetine n=141 Placebo n=139 388/325/256 Atomoxetine n=129 Placebo n=127
Wernicke, 2004 U.S. (Fair)	Visits at weekly intervals assessed CAARS, HAM-D, HAM-A	NR NR NR	Not reported	NR/NR/380 Atomoxetine with abrupt discontinuation n=90; Atomoxetine with tapered discontinuation n=94; Placebo n=196
Spencer, 1998 U.S. (Fair)	Improvement was defined as a reduction in ADHD Rating scale score of 30% or more. Following tests after each arm: ADHD Rating Scale (6) (weekly) Hamilton Depression Rating Scale Beck Depression Inventory Hamilton Anxiety Rating Scale Continuous Performance Test Stroop Tests Wisconsin Card Sorting Test Rey-Osterrieth Complex Figure	n=21 Adults aged 19-60 yrs, 11 women, 10 men, ethnicity NR.	1 lifetime comorbid psychiatric disorder (n=13) current ratings of severe depression or anxiety (n=2) family history of ADHD (n=20) average to above-average intelligence (n=21).	screened NR 22 enrolled Tomoxetine: n=11 Placebo: n=10

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results

Michelson, 2003/Reimherr 2005/Faraone 2005/Spencer 2006 31 outpatient sites in North America, country not otherwise specified (Fair)	71 (25%) withdrew;
	22 (7.8%) lost to fu;
	267 (95%) analyzed (atomoxetine n=133, placebo n=134)
	
	79 (30.9%) withdrew;
	12 (4.7%) lost to fu;
	248 (96.9%) analyzed (atomoxetine m=124,
	placebo n=124)
		Mean change in score, atomoxetine vs placebo, Study I // Study II:
		CAARS-INV total ADHD symptom score -9.5 vs -6.0 (p=0.005) // -10.5 vs -6.7 (p=0.002)
		CAARS-INV Inattentive -5.0 vs -3.1 (p=0.010) // -5.8 vs -3.5 (p=0.001)
		CAARS-INV Hyperactive/Impulsive -4.5 vs -2.9 (p=0.017) // -4.7 vs -3.2 (p=0.013)
		CAARS-Self total ADHD Symptom score -16.0 vs -9.3 (p=0.002) // -17.3 vs -11.6 (p=0.008)
		CAARS-Self inattentive -15.9 vs -8.6 (p<0.001) // -12.5 vs -8.8 (p=0.025)
		CGI-ADHD-S -0.8 vs -0.4 (p=0.010) // -0.9 vs -0.5 (p=0.002)
		WRAADDS -5.3 vs -2.9 (p=0.002) // -4.5 vs -2.8 (p=0.041)
		HAM-D-17 -0.3 vs -0.6 (ns) // +0.2 vs -1.0 (p=0.013)
		HAM-A -1.0 vs -1.2 (ns) // -0.7 vs -1.0 (ns)
		Sheehan Disability total -4.5 vs -2.9 (p=0.022) // -4.4 vs -4.0 (ns)
		Sheehan Disability work life -1.6 vs -1.0 (p=0.007) // -1.8 vs -1.2 (ns)
		Sheehan Disability family life -1.5 vs -1.0 (ns) // -1.4 vs -1.6 (ns)
		Sheehan Disability social life -1.3 vs -0.9 (ns) // -1.2 vs -1.2 (ns)
		
		Spencer 2006 subanalyses of effects of comorbidities
		Predictor of outcome specific to atomoxetine on CAARS subscales: t test/df/p-value
		Investigator-rating Index Subscale:
		Depression NOS: 1.6/494/.121
		MDD: -2.2/500/.028
		Investigator-rating Hyperactivity subscale:
		Depression NOS: 3.9/494/.051
		MDD: -2.1/500/.033
		PTSD: -2.3/505/.020
		Self-rating Hyperactivity Subscale
		PTSD: 3.3/424/.069
		Depression NOS: 2.0/415/.049
		Investigator-rating Inattention subscale
		Depression NOS: -2.1/495/0.35
		PTSD: -2.2/505/.031
		Investigator-rating Total Score
		Depression NOS: 2.2/495/.028
		MDD: -2.0/500/.046
		PTSD: -2.4/505/.016
		Self-rating Total Score

Wernicke, 2004 U.S. (Fair)	2 (0.5%) withdrawn; lost to fu NR; 377 (99.2%) analyzed (atomoxetine-abrupt discontinuation n=89, atomoxetine-tapered discontinuation n=93, placebo n=195)	Change in symptom severity from pretreatment phase to end of treatment phase :: from end of treatment phase to end of discontinuation phase, in atomoxetine abrupt discontinuation vs tapered discontinuation vs placebo: CAARS total score -11.2::5.1 vs -11.4::3.6 vs -7.0::2.7 (ns) HAM-A -0.5::-0.5 vs -1.8::0.2 vs -1.5::0.0 (ns) HAM-D 0.4::-0.5 vs -1.1::0.0 vs -0.9::0.4 (ns) During the discontinuation phase, changes in ADHD symptom ratings did not differ significantly between treatment groups. Depressive or anxiety symptoms did not significantly increase following drug discontinuation, compared with placebo.
Spencer, 1998 U.S. (Fair)	1 withdrawn/ 0 lost to fu 21 analyzed Tomoxetine: n=11 Placebo: n=10	Decrease in ADHD symptoms: tomoxetine: (11/21 subjects)-- week 2: p< 0.01; week 3: p<0.001 (3 week study) placebo: (2/10 subjects). **Results from scales and tests at end of study** reported as: paired tests of tomoxetine scores vs placebo scores; p-value McNemar test: (x= 7.4, df=1; p<0.01) Stroop Color Word test: (z=2.6, n=21, p<0.05) Interference T test scores: (z=2, n=21, p<0.05) ADHD rating scale: p-value= ns

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Michelson, 2003/Reimherr 2005/Faraone 2005/Spencer 2006 31 outpatient sites in North America, country not otherwise specified (Fair)	Elicited by investigator	Atomoxetine vs placebo Dry mouth 21.2 vs 6.8% (p<0.001) Insomnia 20.8 vs 8.7% (p<0.001) Nausea 12.3 vs 4.9% (p=0.003) Decreased appetite 11.5 vs 3.4% (p<0.001) Constipation 10.8 vs 3.8% (p=0.002) Libido decreased 7.1 vs 1.9% (p=0.006) Dizziness 6.3 vs 1.9% (p=0.015) Difficulty attaining or maintaining erection (among males) 9.8 vs 1.2% (p<0.001) Sweating 5.2 vs 0.8% (p=0.004)	Atomoxetine vs placebo: Total withdrawals: 73 (27%) vs 55 (20.7%), (ns) Withdrawals due to AEs: 23 (8.5%) vs 9 (3.4%), (p=0.03)
Wernicke, 2004 U.S. (Fair)	Elicited by investigators, via open-ended questioning, and the Association for Methodology and Documentation in Psychiatry-5: Somatic Signs	% in atomoxetine-abrupt vs atomoxetine-tapered vs placebo: Headache 4.4 vs 10.6 vs 4.1% (ns) Pain in limb 3.3 vs 1.1 vs 0% (p=0.019) Diarrhea 2.2 vs 5.3 vs 2.6% (ns) Sinusitis 2.2 vs 4.3 vs 0.5 (ns) Insomnia 1.1 vs 5.3 vs 3.1 (ns) Irritability 0 vs 4.3 vs 0% (p=0.007) Dyspepsia 0 vs 4.3 vs 0.5% (ns) Allergic reactions: 1.1 vs 6.5 vs 1.5% (p=0.036)	Atomoxetine-abrupt vs atomoxetine-taper vs placebo: Total withdrawals: 0 vs 1 (1%) vs 1 (0.5%) Withdrawals due to AEs: 1 (1%) in atomoxetine-taper discontinuation phase, due to headache
Spencer, 1998 U.S. (Fair)	self-report from patients	no serious adverse events observed, 1 subject withdrawn after becoming ery anxious on tomoxetine.	tomoxetine: 1/21 (due to increased anxiety in patient) placebo: 0 withdrawals;

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Michelson, 2003/Reimherr 2005/Faraone 2005/Spencer 2006 31 outpatient sites in North America, country not otherwise specified (Fair)	
Wernicke, 2004 U.S. (Fair)	Depressive or anxiety symptoms did not significantly increase following drug discontinuation.
Spencer, 1998 U.S. (Fair)	3 week study period.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Adler 2006					

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Adler 2006				

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results
Adler 2006		

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Adler 2006			

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Adler 2006	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Bupropion					
Wilens, 2001 U.S. (Fair)	DB RCT parallel groups	Subjects were outpatient adults with ADHD aged 20-59, recruited from advertisements and clinical referrals to a psychopharmacology clinic. To obtain a full diagnosis of adult ADHD, the subject had to have 1) fully met the DSM-IV criteria for ADHD by age 7 as well as currently (within the past month); 2) described a chronic course of ADHD symptoms from childhood to adulthood, and 3) endorsed a moderate or severe level of impairment attributed to those symptoms.	Bupropion SR 200-400 mg/day, taken upon awakening and 6 hours later. Dose was titrated over 4 weeks, beginning at 100 mg bid, and increased by 100 mg weekly up to 200 mg bid in week 4. Bupropion mean dose at week 6: 362 mg/day. Weekly supplies of bupropion and placebo were dispensed in 100-mg capsules. Placebo mean dose at week 6: 379 mg/day Duration 6 weeks	NR/NR	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Bupropion				
Wilens, 2001 U.S. (Fair)	CGI Severity and Improvement scales, and the ADHD Rating Scale were administered at baseline and weekly visits. HAM-D, BDI, and HAM-A were administered at baseline and end of study. Categorical improvement was defined as a reduction in ADHD Rating Scale score of 30% or better.	Mean age 38.3 55% male Ethnicity NR	Inattentive subtype 58% Combined subtype 35% Hyperactive or impulsive subtypes 8% Major depression: past 59%, current 19% Two or more anxiety disorders: past 19%, current 8% Substance abuse/dependence: past 35%, current 0% Smoking: past 33%, current 10% Alcohol abuse/dependence: past 33%, current 10% Antisocial personality disorder: past 16%, current 0%	154/NR/40 Bupropion n=21 Placebo n=19

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results
Bupropion		
Wilens, 2001 U.S. (Fair)	2 (5%) withdrawn; 0% lost to fu; 40 (100%) analyzed: Bupropion n=21, Placebo n=19	Bupropion vs placebo: CGI improvement rating of 1 (much improved) or 2 (very much improved): 52 vs 11%, p=0.007 Improved by 30% or more reduction in DSM-IV ADHD symptom checklist score: 76 vs 37% (p=0.02) Mean change from baseline to 6 weeks in ADHD symptom checklist score: -42% vs -24% (p=0.05) Proportion of the 18 DSM-IV ADHD-specific symptoms that improved: 100 vs 44% (p<0.001) Depression and anxiety (HAM-D, BDI, HAM-A): no difference between groups

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Bupropion			
Wilens, 2001 U.S. (Fair)	Elicited by investigator at each visit	Bupropion vs placebo: Headache 19 vs 16% (ns) Aches or pains 10 vs 5% (ns) Dry mouth 10 vs 0% (ns) Chest pain 10 vs 0% (ns)	Bupropion vs placebo, Total withdrawals: 2 (9.52%, noncompliance) vs 0% Due to AEs: 0 vs 0

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Bupropion	
Wilens, 2001 U.S. (Fair)	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Dexamphetamine					
Paterson, 1999 Australia (Fair)	DB RCT parallel groups	Patients were eligible if they reported the presence of at least 4 inattentive and/or 5 hyperactive symptoms during the previous 6 months. Screening for illicit substance use among eligible patients was conducted by urinalysis.	Dexamphetamine mean dose 4.77 tablets per day (23.85 mg/day); Placebo. Dose was titrated gradually throughout the study. Week 1: 1 tablet in AM, Week 2: 1 tablet in AM and 1 tablet at noon, Week 3: 1 tablet in AM and 2 tablets at noon, Weeks 4-6: up to 6 tablets per day, but increased by no more than 1 tablet per day, with 2 days between increases. Duration 6 weeks	NR/NR	NR
Dextroamphetamine					
Weiss 2006	DB RCT	Outpatients age 18 to 66 years diagnosed ADHD via DSM IV	Placebo , Paroxetine (Par), Dextroamphetamine (Dex) and Par + ex, titrated for 4 weeks up to Par 40 mg/day and Dex 40 mg day Dration 20 weeks	1 week washout	No but all received psychotherapy
Methylphenidate IR					
Barkley 2005 United States	DB RCT crossover		Methylphenidate 10 mg, single dose (low dose) Methylphenidate 20 mg, single dose (high dose) Placebo Subjects were crossed over to each dose one time (ie, all subjects took one dose of each of the three interventions), 75 minutes before testing began	NR/ at least a 24 hr washout period for stimulant medication before testing	allowed all other medications but stimulants
Bouffard, 2003 Canada (Fair)	DB RCT crossover design	DSM-IV diagnosis of ADHD; 1.5 or more on at least 1 ADHD self-report questionnaire (either CAARS or AAPBS); IQ >=80 on abbreviated WAIS-R	Methylphenidate or placebo (sugar pill) 30 mg/day for 2 weeks (10 mg tid,) followed by 45 mg/day for 2 weeks (15 mg tid). Subjects were randomly assigned to start either methylphenidate or placebo.	3-day run-in of increasing dosages (15/30/45 mg/day); 5 to 7-day washout btw. active & placebo phases	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Dexamphetamine				
Paterson, 1999 Australia (Fair)	DSM-IV ADHD criterion list with modified thresholds (see comments) were administered at baseline, 3 weeks, and 6 weeks. Patients' relatives were also asked to fill out these questionnaires for comparison. Patients completed the BSI, a 53-item self-report symptom inventory, at baseline and weeks 3 and 6. Three CGI subscales were used at baseline and week 6: Severity at baseline, Improvement at 6 weeks, and an Efficacy Index was calculated by using a ratio of benefits against side effects. Patient satisfaction was measured at the end of the trial on a 5-point Likert Scale.	Mean age 35.5 60% male Ethnicity NR	51% were inattentive type 46.7% were combined inattentive and hyperactive types 2% were hyperactive type	68/51/45 24 dexamphetamine 21 placebo
Dextroamphetamine				
Weiss 2006	ADHD-RS Investigator version CGI-I	Mean age 37.5 64% male Ethnicity 85% white	53% lifetime mood or anxiety disorder	144/129/98 Placebo 26 Par 24 Dex 23 Par + Dex 25
Methylphenidate IR				
Barkley 2005 United States	These results were measured at baseline, and at the end of each of the three drug conditions (ie, on the same day as the testing occurred): *Conners continuous performance test (measuring number of omissions and reaction time for inattentiveness and false hits and reaction time for impulsiveness) *FAAC virtual reality driving simulator: each time a series of 5 tests were given (daytime course #1, nighttime course #1, daytime course #2, nighttime course #2, and an obstacle course). Courses #1 and #2 took approximately 12 minutes to complete. *Examiner rating of simulator driving performance *Patient self-rating of simulator driving performance	Mean age: 31.3 years (SD: 11.3) 74% male White: 83.3% African American: 3.7% Hispanic: 5.6% Native American: 5.6% Other: 1.9%	Combined subtype: 87% Predominantly Inattentive subtype: 11% Predominantly Hyperactive-Impulsive subtype: 0% ADHD not otherwise specified: 2% Never married: 67% Mean IQ: 104.7 (SD=9.7) Average number of years of driving experience: 14.5 years (SD: 11.1) Mean number of miles driven/week: 252 miles (SD: 203)	56 / 56 / 54 Same subjects exposed to all treatments
Bouffard, 2003 Canada (Fair)	2 self-rating questionnaires (CAARS & AAPBS); SCL-90, BDI, HAM-A; GAF	Mean age 34 80% male Ethnicity NR	Mean IQ 101	93/NR/38 Same subjects exposed to both treatments

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results
Dexamphetamine		
Paterson, 1999 Australia (Fair)	1 (2.2%) withdrawn 0% lost to followup 45 (100%) analyzed: Dexamphetamine n=24, Placebo n=21	Mean change in score from 0 to 6 weeks, p-values signifying change from baseline, dexamphetamine vs placebo: ADHD score, Hyperactive -2.0 (p=0.004) vs -1.0; Inattentive -3.83 vs -1.57 (ns); Total -5.83 (p<0.0001) vs -3.57 (p=0.042) BSI mean T-score, Anxiety -8.2 (p<0.001) vs -5.43 (p<0.001); Depression -3.59 (ns) vs -2.76 (ns); Global Severity Index -5.5 (ns) vs -6.19 (ns) Efficacy Index at week 6: 95% of placebo had equal levels of benefits and side-effects; 75% of dexamphetamine had greater benefits than side-effects (p<0.001)
Dextroamphetamine		
Weiss 2006	34/NR/98 Placebo 26 Par 24 Dex 23 Par + Dex 25	Response CGI-I Much or very much improved Placebo 28% Par 65.2% Dex 63.6% Par+Dex 56% Response CGI-I-ADHD Much or very much improved Placebo 16% Par 63.6% Dex 44% Par+Dex 44% Response CGI-I for mood and anxiety disorder Much or very much improved Placebo 36% Par 69.6% Dex 45.5% Par+Dex 48%
Methylphenidate IR		
Barkley 2005 United States	2 / 0 / 52 had complete data	Mean results for 1-baseline vs 2-MPH low vs 3-MPH high vs 4-placebo Standard course: Simulator self-rating: 55.7 vs 60.6 vs 61.9 vs 61.4 (p<0.001; pair-wise contrasts: 1<2,3,4) Simulator observer rating: 54.4 vs 60.1 vs 59.7 vs 59.2 (p<0.001; pair-wise contrasts: 1<2,3, 4) Number of crashes: 1.7 vs 0.9 vs 0.7 vs 0.9 (p<0.001; pair-wise contrasts: 1>2, 3, 4) Average speed and speed variability were not significantly different between groups; steering variability, course driving time, and number of turn signals given were significant between groups, but none showed a significant difference between MPH low and MPH high Only 44 of 54 patients could complete the obstacle course Conners Continuous performance test: Comission Errors: 13.3 vs 7.5 vs 7.2 vs 8.5 (p<0.001; pair-wise contrasts: 1>2, 3, 4; 4>3) Omission Errors: 4.2 vs 3.2 vs 2.0 vs 2.8 (not significantly different) Reaction time and reaction time variability did not differ significantly between the four groups
Bouffard, 2003 Canada (Fair)	8 (21%) withdrawn Loss to followup NR 30 (79%) analyzed, same subjects exposed to both treatments (phases were combined in analysis)	Mean change in condition from baseline, methylphenidate 30 mg/day vs methylphenidate 45 mg/day vs placebo (*p-values compare placebo with methylphenidate*): Adult behavior problems -1 vs -1 -0.7 (p<0.005) CAARS -0.8 vs -0.9 vs -0.5 (p<0.01) CPT% commission error -17.1 vs -19.4 vs -9.8 (p<0.001) CPT% omission error -3.3 vs -3.0 vs -0.5 (p<0.1) Stop-signal task vs -35.8 vs -47 vs -29.05 (ns) HAM-R -0.4 vs -0.5 vs -0.35 (p<0.05) BDI -5.5 vs -5.5 vs -4.4 (ns) SCL-90-R -9.8 vs -11 vs -7.45 (ns) Obsessive-compulsive scale -12 vs -13 vs -7.5 (p<0.05) Hostility scale -6.0 vs -6.8 vs -3.5 (ns)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Dexamphetamine			
Paterson, 1999 Australia (Fair)	Weight loss and evaluation of blood pressure were assessed at weeks 3 and 6. Urinalysis was conducted at baseline and weeks 6 to ensure compliance and exclude drug abuse. Patients kept a diary of side effects.	Dexamphetamine vs placebo, number of patients: Sleep disturbance: 9 vs 1 Headache: 6 vs 3 Dry mouth: 7 vs 0 Thirst: 3 vs 0 Mean weight loss: -3.6 kg (p<0.001) vs -0.286 kg (ns)	Dexamphetamine vs placebo, Total withdrawals: 1 (4.2%) vs 0% Due to AEs: 1 (4.2%, depression) vs 0%
Dextroamphetamine			
Weiss 2006	Collected at study visits, rated as mild, moderate and severe	83% of patients reported at least one AE	Total withdrawals: Placebo 5 Par 9 Dex 9 Par+Dex 10 Due to AEs: Placebo 2 Par 6 Dex 3 Par+Dex 7
Methylphenidate IR			
Barkley 2005 United States	Self-rated and observer rated simulator sickness	the only AE reported was for simulator sickness.	Crossover design, thus withdrawals by treatment not given; unclear if patients who withdrew for part of a test completed the rest of the crossovers
Bouffard, 2003 Canada (Fair)	Self-rated	Change from baseline in % of subjects reporting condition, methylphenidate 45 mg/day vs placebo: Mild appetite loss +23 vs +5% (ns) Mild trouble sleeping -2 vs -7% (ns) Moderate trouble sleeping -13 vs -9% (ns) Mild headache -4 vs +5% (ns)	Methylphenidate vs placebo, Total withdrawals unclear by treatment group; 4 enrolled withdrew on mehtylphenidate "because they were not blind" to treatment. Withdrawals due to AEs (n=1, (2.6%), treatment group unclear.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Dexamphetamine	
Paterson, 1999 Australia (Fair)	The report does not state the dose of dexamphetamine, only the number of tablets. The dose of 5 mg in each tablet was inferred from other publications using Sigma's preparation of dexamphetamine in Australia.
Dextroamphetamine	
Weiss 2006	
Methylphenidate IR	
Barkley 2005 United States	All subjects were paid $150 at the end of the protocol.
Bouffard, 2003 Canada (Fair)	Data from the first treatment phase was not reported separately. Concealment of allocation is a concern: "Not blind to methylphenidate," caused 6 pre-enrollment and 4 post-enrollment exclusions. The hospital pharmacy used a numbered list for allocation; subjects gave their number to the pharmacist when picking up prescriptions. Run-in rapidly titrated to maximum trial dose in 3 days, but withdrawals from side effects was not high (n=1).

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Cox, 2000 U.S. (Fair)	DB RCT crossover design	ADHD and non-ADHD male subjects with no other current comorbidity were recruited from the local community from TV and computer bulletin board notices, as well as direct physician referrals. ADHD subjects were required to have previously taken Ritalin, but could not be taking any medication for their condition within the past 6 months. To confirm DSM-IV criteria for ADHD, participants were interviewed using Barkley's structured interview for ADHD and the DSM-III-R criteria. ADHD subjects had current and childhood symptoms, consistent with DSM-III-R criteria.	Methylphenidate 10 mg/day, single dose Placebo (vitamin C), single dose Subjects were admitted to the research center to control for diet and sleep conditions. On the following day at 8AM, subjects received either placebo or methylphenidate at 8AM. 1.5 hours after taking the medication, subjects drove for 30 minutes on a simulator. At 3:30PM, subjects received the alternative treatment (placebo or methylphenidate) than that received at 8AM. 1.5 hours after taking the medication, subjects drove for 30 minutes on a simulator using an alternative driving scenario.	NR/NR	NR
Gualtieri, 1985 U.S. (Fair)	DB RCT crossover design	Eight male subjects who met the diagnostic criteria for ADD-RT. Subjects had clinical histories consistent with ADHD during their primary school years, which were confirmed by parents and by review of medical or school records. All subjects continued to have difficulty with poor attention span and distractibility, restlessness and fidgety behavior, impulsiveness, emotional lability (especially temper outbursts), unsatisfactory level of efficiency at work, and difficult interpersonal relationships.	MPH (0.3 mg/kg) or Placebo were given on a bid schedule (8AM and 12 noon) for 5 days (Monday through Friday). On the second Monday, following a 68-hr washout period, the procedure was repeated with the alternative treatment.	Run-in NR; 68-hr washout between treatment phases	NR
Kinsbourne, 2001 U.S. (Fair)	DB RCT crossover design	Subjects were selected from consecutive adult clinic referrals based on the following: 1) history of symptoms meeting DSM-IV ADHD (at least 6 of 9 inattentive and/or hyperactive/impulsive symptoms); 2) full DSM-IV criteria for ADHD met in childhood, in retrospect; 3) have no other psychiatric disorder that would explain their symptoms of ADHD; 4) gave informed consent.	Methylphenidate 5, 10, and 20 mg/day Placebo Each dose of MPH or placebo was administered in a single dose, in a randomized sequence, in the morning on each of four days. Duration 4 days	NR/NR	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Cox, 2000 U.S. (Fair)	The Atari Research Driving Simulator had 2 equivalent driving courses with similar driving demands. The 16-mile courses take approximately 30 minutes to complete when following posted speed limits. The simulator quantifies steering, braking, and crash variables. After completing the simulation, subjects were asked to rate their driving performance on a 5-point scale (1=poor, 5=well).	Mean age 22.0 100% male 77% white 15% black 7.7% Asian	ADHD patients vs non-ADHD controls: Mean # motor vehicle violations, 2.6 vs 1.5 (p=0.06) Mean # automobile crashes, 2.7 vs 0.8 (p=0.018)	NR/NR/13 Same subjects exposed to both treatments
Gualtieri, 1985 U.S. (Fair)	On the first day of each treatment phase, a nurse measured pulse and blood pressure in seated subjects, and a blood sample was drawn to measure baseline growth hormone (GH) levels. 1 hour after the first dose of MPH or placebo, pulse and blood pressure were again measured, followed by a second blood sample for MPH serum levels and GH. Subjects then completed the CPT with a wristwatch actometer on the nondominant arm. At the end of each treatment phase, subjects filled out the AAS, ZSDS, and ZSAS and reported their subjective experiences. Before the drug code was broken, subjects were asked to guess which drug was MPH and which was placebo.	Mean age 27.2 100% male Ethnicity NR (represents n=22, of which 8 were included in the placebo-RCT)	In the total sample (n=22, of which 8 participated in the DB RCT), previous diagnoses included depressive neurosis (n=3), personality disorder (n=3), and alcoholism (n=1). Two subjects had narcolepsy.	NR/NR/8 Same subjects exposed to both treatments
Kinsbourne, 2001 U.S. (Fair)	CPALT - 30-minute test, 4 sessions. On each day of assessment, patient was tested at time zero (baseline), 2 hours after drug administration, in a randomized sequence, counterbalanced across subjects. Favorable response was defined as performance on one of the drug conditions 25% or more above that on placebo. Adverse response was 25% below placebo. Outcomes between those extremes was recorded as non-response.	Mean age 34 41.2% male Ethnicity NR	None of the subjects had been previously diagnosed with ADHD, and none were currently taking psychoactive drugs.	NR/NR/17 Same subjects exposed to all treatments

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results
Cox, 2000 U.S. (Fair)	0% withdrawn; 0% loss to followup; 13 (100%) analyzed, same subjects exposed to both treatments (phases were combined in analysis)	Placebo vs ritalin, mean Impaired Driving Score (score of 0 would be average, +1 would be one standard deviation worse than the mean): ADHD patients +0.5 vs +2.4 (p=0.05) Non-ADHD controls +0.6 vs -1.0 Mean self-rated driving performance, ADHD patients vs non-ADHD controls: Placebo: 3.0 vs 3.9 (p=0.05) Ritalin: 3.5 (+0.5 better than placebo) vs 3.6 (-0.3 worse than placebo), (ns)
Gualtieri, 1985 U.S. (Fair)	NR/NR/8 N per drug not reported (phases were combined in analysis).	Placebo vs MPH: AAS: 27.7 vs 25.8, NS ZSDS: 45.3 vs 37.5, NS ZSAS: 38.3 vs 33.8, NS CPT correct: 121.8 vs 128.5, p <0.05 CPT errors: 5.3 vs 2.1, NS Actometer: 98.6 vs 60.3, NS Growth hormone: 1.3 vs 6.0, NS MPH significantly imporved correct responses on the CPT. All subjects accurately guessed the active drug condition.
Kinsbourne, 2001 U.S. (Fair)	0% withdrawn 0% lost to followup 17 (100%) analyzed; N per drug not reported (phases were combined in analysis)	12% were non-responders; their best performance was on placebo. 88% were favorable responders; 41% performed optimally at 5 mg; 12% at 10 mg; 35% at 20 mg

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Cox, 2000 U.S. (Fair)	NR	NR	Methylphenidate vs placebo, Total withdrawals: 0 vs 0 Withdrawals due to AEs: 0 vs 0
Gualtieri, 1985 U.S. (Fair)	NR	AEs were not reported among the 8 subjects who participated in the short-term DB RCT.	Methylphenidate vs placebo, Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0
Kinsbourne, 2001 U.S. (Fair)	NR	NR	Methylphenidate (5/10/20 mg/day) vs placebo, Total withdrawals: 0/0/0 vs 0. Withdrawals due to AEs: 0/0/0 vs 0

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Cox, 2000 U.S. (Fair)	Data from the first treatment phase was not reported separately. Author concludes that Ritalin improved ADHD driving performance to the non-ADHD level.
Gualtieri, 1985 U.S. (Fair)	Despite small sample size (n=8), MPH improved correct responses on CPT to a statistically significant degree. Levels of growth hormone were non-significantly higher on MPH than placebo.
Kinsbourne, 2001 U.S. (Fair)	Data from the first treatment phase was not reported separately.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Kooij 2004 Netherlands	DB RCT crossover	Outpatient adults with ADHD aged 20 to 56 years, with current ADHD (at least 5 of 9 symptoms of inattention and/or hyperactivity /impulsivity) and childhood onset with at least 6 of 9 symptoms in one or both symptom domains.	Methylphenidate and placebo. MPH was started at 0.5 mg/kg/day by week 1, increased to 0.75 mg/kg/d by week 2, and was uptitrated to 1.0 mg/kg/d by week 3 unless adverse events emerged. Treatment was 3 weeks long. There were two 3-week treatment periods with 1 week of washout in-between the crossover.	NR / 1 week washout between treatment crossover	NR
Boonstra 2004 Netherlands cognitive outcomes from Kooij 2004	DB RCT crossover	see Kooij above	see Kooij above For the 43 patients analyzed in this paper, the mean daily dose of MPH was 70.6 mg (SD: 16.7) Mean dose mg/kg/d was 0.93 mg/kg/d (SD: 0.18)	see Kooij above	NR
Mattes, 1984 U.S. (Fair)	DB RCT crossover design	Subjects were drawn from a psychiatric outpatient clinic and via newspaper ads and given a questionnaire of 5 ADD symptoms (restlessness, difficulty concentrating, excitability, impulsivity, irritability). Subjects were aged 18-45, who met questionnaire criteria and received a psychiatrist rating of at least 2 on at least 3 of the 5 adult ADD symptoms. Subjects with history of childhood ADHD were assigned to experimental group; subjects with no childhood history were assigned to control group.	Methylphenidate or placebo: dosage began at 5 mg bid (8AM and 12 noon), increased to 10 mg bid every 2 days, to a maximum of 30 mg bid. Methylphenidate mean dose: 48.2 mg/day Placebo mean dose: 57 mg/day Sequence of drug phases was randomized. Each phase lasted three weeks, with no intervening washout period.	NR/NR	NR; drug or alcohol abuse was allowed

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Kooij 2004 Netherlands	Symptoms of ADHD measured with Dutch self-report version of the DSM-IV ADHD rating scale Severity of ADHD measured with CGI - ADHD Depression was measured with Hamilton Depression Scale (HAM-D) Anxiety was measured with Hamilton Anxiety Scale (HAM-A) Functional impairment measured using the Dutch version of the Sheehan Disability Scale (SDS) and the Global Assessment of Functioning scale (GAF) All assessments were made at baseline and at the end of the first and second treatment period, except for the DSM-IV ADHD rating scale, the CGI-ADHD and the adverse events list (all of these were administered weekly). The primary outcome was a decrease of ≥2 points on theCGI-ADHD scale over the total treatment period (3 weeks) + a ≥30% symptom reduction in the DSM-IV ADHD rating scale.	Mean age: 39.1 years 53.3% male Ethnicity: NR	95.5% had ADHD combined subtype 4.5% had ADHD hyperactive / impulsive subtype Average IQ: 101 (SD: 18) School failure: 76% Sheehan Disability scale (min 0, max 30): 22.8 (SD: 3.3) Global Assessment of Functioning (min 0, max 100): 57.3 (SD: 6.1) Co-morbid Antisocial or Borderline Personality Disorder: 33% Baseline HAMD: 8.0 (SD: 5.8) Baseline HAMA: 7.8 (SD: 6.0) Any substance use disorder: 51%	NR / 108 / 45 same subjects exposed to both treatments
Boonstra 2004 Netherlands cognitive outcomes from Kooij 2004	Conners' Continuous Performance Test (CPT) Change Task (ChT) of Logan and Burkell (computerized) Tests were given at the end of week 3 and the end of week 7 (ie, when MPH was at its highest). Tests were given in random order, and were given 75 minutes after tablet intake.	(these are statistics for the 43 who completed the trial without protocal violations) Mean age: 38.9 years 48.8% male Ethnicity: NR	(these are statistics for the 43 who completed the trial) 95.3% had ADHD combined subtype 4.7% had ADHD hyperactive / impulsive subtype Average IQ: 100.3 (SD: 17.9) Sheehan Disability scale (min 0, max 30): 22.8 (SD: 3.3) Global Assessment of Functioning (min 0, max 100): 57.3 (SD: 6.1) Antisocial Personality Disorder: 9.3% Borderline Personality Disorder: 16.3%	NR / 108 / 45
Mattes, 1984 U.S. (Fair)	To determined childhood history of ADHD, patients completed questionnaires including items from CTQ; if a parent was accessible, the parent was asked to quantitate the patient's childhood behavior (CPQ); a relative was asked to complete a modified version of the adult ADD questionnaire; and school records were requested. Patient and psychiatrist rated global improvement weekly; self-rated adult ADD questionnaire, SCL-90, POMS completed at weeks 3 and 6. A study psychiatrist completed a structured interview form of 23 ratings of adult ADD symptoms.	NR NR NR	29 patients with childhood ADHD 37 patients without childhood ADHD DSM-III diagnoses of subjects: ADD residual type 42.4% Antisocial personality disorder 7.6% Alcoholism 10.6% Drug abuse 24.2% Borderline personality disorder 24.2% Major depressive episode (mild) 28.8% Generalized anxiety disorder 10.6% Other 68.2%	2829/116/66 Same subjects exposed to both treatments

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results
Kooij 2004 Netherlands	0 / 0 / 45 same subjects exposed to both treatments	% of responders at end of treatment periods, methylphenidate vs placebo: DSM-IV ADHD rating scale combined with CGI-S: 38% vs 7%, p=0.003 DSM-IV ADHD rating scale only: 42% vs 13%, p=0.011 CGI-S scale only: 51% vs 18%, p=0.011 Compliance data (taking medicine >80% of time; for 41 patients): 68.3% compliant 31.7% non-compliant Mean decrease in scores for methylphenidate vs placebo, p-value: DSM-IV ADHD: -0.19, p=0.064 CGI-S: -0.72, p=0.026 SDS: -0.93, p=0.029 GAF score: +2.5, p=0.104 HAMD: +2.4, p=0.002 (ie, MPH is associated with higher symptom leves of depression) HAMA: +2.9, p=0.002 (ie, MPH is associated with higher symptom leves of anxiety)
Boonstra 2004 Netherlands cognitive outcomes from Kooij 2004	2 / 0 / 43 43 subjects exposed to both treatments. This analysis excluded two patients who were included in the Kooij analysis.	Mean test results, MPH vs placebo: CPT: Mean hit reaction time: 342.6 vs 333.5, p=0.029 Standard error: 4.9 vs 6.0, p=0.11 Commission errors: 10.7 vs 13.6, p=0.002 Attentiveness: 3.4 vs 3.1, p=0.007 Risk taking: 0.7 vs 0.6, p=0.837 Change Task variables, over all 7 weeks: (univariate tests revealed significant interactions of treatment condition and treatment order for mean reaction time (p=0.001) and standard deviation of reaction times (p=0.000)) Stop signal reaction time: 202.3 vs 220.0, p=0.87 Change response mean reaction time: 457.1 vs 475.3, p=0.033 Change response standard deviation reaction time: 113.2 vs 117.0, p=0.615 data for the first point of measurement (after 3 weeks) for the variables showing the significant interactions between treatment order and treatment condition: Mean reatction time: 407.4 vs 434.1, p=0.346 Standard deviation reactin time: 78.2 vs 96.9, p=0.52
Mattes, 1984 U.S. (Fair)	5 (7.6%) withdrawn; Loss to followup NR; 61(92.4%) analyzed; N per drug not reported (phases were combined in analysis).	No response to methylphenidate occurred in either patients with or without childhood ADHD. Results among patients without childhood ADHD were n shown. Psychiatrist-rated improvement (1=completely recovered; 8=much worse) among patients with varying certainties of having had childhood ADHD, methylphenidate vs placebo: Definitely (at least 90% certainty), N=2: 5.0 vs 4.00 (ns) Very likely (at least 70% certainty), N=16: 4.19 vs 4.31 (ns) Probably (at least 50% certainty), N=26: 4.42 vs 4.58 (ns)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Kooij 2004 Netherlands	Side effects measured using a modified version of the Side Effects Rating Scale from Barkely (Barkley and Murphy 1998)	Methylphenidate vs placebo: % of patients on treatment reporting any AEs: 82% vs 69% (p=0.11) Loss of appetite: 22% vs 4 % (p=0.039) Sleeping problems: 33% vs 22% (p=0.27) Headache: 16% vs 4% (p=0.18) Tachycardia: 9% vs 2% (p=0.25) Dizziness: 16% vs 7% (p=0.34) Abdominal complaints: 13% vs 4% (p=0.22) Dry mouth: 24% vs 7% (p=0.06) Tics: 7% vs 2% (p=0.5) 18% of patients lowered their MPH dose due to AEs; none dropped out due to AEs Systolic blood pressure: +0.13 mmHg after MPH (p=0.954) compared to placebo Diastolic pressure "virtually unchanged" Mean heart rate: +4.8 beats/min higher after MPH (p=0.002) compared to placebo Mean body weight: -1.7kg after MPH (p<0.001) compared to placebo	0 / 0
Boonstra 2004 Netherlands cognitive outcomes from Kooij 2004	see Kooij above	see Kooij above	see Kooij above
Mattes, 1984 U.S. (Fair)	SADS-C elicited by investigator	The following AEs occurred significantly (p<0.05) with methylphenidate: more anorexia, headaches, late-afternoon depression, and less psychiatrist-rated impulsivity. Numeric results for AEs were not shown.	Methylphenidate vs placebo: Total withdrawals unclear by treatment group; Withdrawals due to AEs not reported.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Kooij 2004 Netherlands	Exclusion criteria included: clinically unstable psychiatric conditions, current use of psychotropics, prior use of methlyphenidate or amphetamines, and a history of tic disorders.
Boonstra 2004 Netherlands cognitive outcomes from Kooij 2004	This analysis did not analyze data from 2 non-compliant patients who were included in the original paper (see Kooij 2004).
Mattes, 1984 U.S. (Fair)	This study included adults with ADD symptoms, with or without ADHD in childhood. Outcomes represent 26 patients with childhood ADHD; AEs reflect the experience of all study subjects. Data from the first phase was not reported separately.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Schubiner, 2002 U.S. (Fair)	DB RCT parallel groups	Between the ages of 18 and 55 years; DSM-IV criteria for current cocaine dependence; provide a urine specimen with a positive urine toxicology result for cocaine metabolite; meet criteria for the diagnosis of ADHD as a child and as an adult	Methylphenidate 30 mg/day for first 2 or 3 days; 60 mg/day for the next 4 to 5 days; 90 mg/day by day 8 Placebo Plus twice-weekly cognitive-behavioral group therapy (CBT) for cocaine dependence Pemoline arm dropped after the first year because of recruitment difficulties Dosing: three times daily (times nr) Duration: 13 weeks	NR/NR	NR
Spencer, 1995 U.S. (Fair)	DB RCT crossover design	Male or female aged 18-60, with at least 8 of 14 DSM-III-R criteria for ADHD (assessed by psychiatric evaluation and structured diagnostic interview), with onset in childhood by age 7, chronic course until time of assessment, and associated with significant distress and disability. Adults were self-referred or referred by other clinicians for life-long histories of inattention and underachievement.	Randomized crossover design of methylphenidate vs placebo, with 1 week washout between treatment phases; total trial duration 7 weeks. Study medication was titrated up to 0.5 mg/kg per day by week 1, 0.75 mg/kg/day by week 2, and up to 1.0 mg/kg/day by week 3.	Run-in NR; 1-week washout between phases	NR
Spencer, 2005 U.S. (Poor)			Randomized parallel design of methylphenidate vs placebo. Total trial duration: 6 weeks. Study medication was titrated up to 0.5 mg/kg per day by week 1, 0.75 mg/kg/day by week 2, and 1.0 mg/kg/day by week 3.	NR/NR	Other psychoactive medications were not permitted

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Schubiner, 2002 U.S. (Fair)	ADHD outcome measures (administered at weeks 5, 9 and 13) ADHD Symptom Checklist Global Improvement Scale Beck Depression Inventory Substance use outcomes Urinalysis Addiction Severity Index (ASI) - every visit Tiffany Cocaine Craving Scale - monthly Self-report - beginning of each study week	Mean age=37.5 89.6% male 70.8% white	No. days using cocaine in last 30 days=13.52 No. hyperactive symptoms=5.8 No. inattentive symptoms=4.8 Mean BDI scores=22.4 ASI Drug use=0.2242 Alcohol use=0.1605 Illegal activity=0.1172 Medical condition=0.1080 Family relations=0.3047 Psychiatric status=0.3324 Employment=0.4503 Affective disorders=56% Anxiety disorders=12.5% Other Axis I disorders=4.1%	932/338/59 Methylphenidate n=24 Placebo n=24 Pemoline n=11 (dropped from analysis)
Spencer, 1995 U.S. (Fair)	Improvement defined as CGI score less than 2 and a reduction of at least 30% in individual rating scale scores. HAM-D, HAM-A, BDI before and after each arm of the study. CGI and ADHD rating scale administered weekly.	Mean age 40 43.5% male 100% white non-Hispanic	74% had at least one past comorbid psychiatric disorder 56% had a current comorbid psychiatric disorder	85/25/25 N per drug during first phase not reported.
Spencer, 2005 U.S. (Poor)	Primary outcome: Adult ADHD Investigator System Report Scale (AISRS) and Clinical Global Impression (CGI) Scale. Responder status was defined as a 30% reduction in the AISRS plus "much" or "very much improved" in the CGI. Timing: weekly Secondary outcome: Hamilton Depression Scale; Beck Depression Inventory; Hamilton Anxiety Scale. Timing: at the begining and end of the study	Mean age 37 58.2% male Ethnicity: NR	38% major depression 9% multiple (>2) anxiety disorders	289/NR/146 104 in MPH; 42 in placebo

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results
Schubiner, 2002 U.S. (Fair)	34 (57.6%) withdrawn; 11 (18.6%) dropped due to being in the pemoline group; Lost to fu NR; 48 (100% for MPH vs placebo comparison) for most efficacy measures MPH n=24, placebo n=24	MPH vs placebo (mean change); differences NS unless otherwise specified No. inattentive symptoms=2.13 (-2.79) vs 2.83 (-1.96) No. hyperactive symptoms=3.42 (-2) vs 4.78 (-1.47) No. days using cocaine in past 30 days=15.42 (+2.13) vs 14.58 (+0.83) Amount spent on cocaine in past 30 days=$62.54 vs $97.19 Longest continuous abstinence=5.17 vs 5.17 % Urine samples tested negative for cocaine=0.5 vs 0.42 Physician efficacy ratings showing moderate improvement: 77% vs 21%, p<0.05 at 4 weeks: 77% vs 44% at 8 weeks: 60% vs 36% at 12 weeks: 50% vs 56% last visit: 73% vs 42%, p<0.05 Mean participant efficacy ratings at last visit: 1.88 vs 2.68; p<0.05 at 4 weeks: 2.57 vs 3.00 at 8 weeks: 2.08 vs 3.08 at 12 weeks: 1.75 vs 2.64
Spencer, 1995 U.S. (Fair)	2 (8%) withdrawn 0% lost to followup 23 (92%) analyzed. N per drug in 1st treatment phase not reported.	Mean change in score during first treatment phase (Weeks 1-3), methylphenidate vs placebo: ADHD Rating Scale -18 vs -2.5 (p<0.0001) Global Severity subscale of the CGI Scale -1.8 vs 0 (p<0.0001) Mean change in ADHD symptom cluster score, using 1st and 2nd treatment phases combined, methylphenidate vs placebo: Hyperactivity overall -1.2 vs -0.16 (p<0.001) Impulsivity overall -1.3 vs -0.44 (p<0.001) Inattentiveness -0.62 vs -0.26 (p<0.001) % of patients who improved, ie. CGI score <2 and reduction >=30% in individual rating score: 78% vs 4% (p<-0.001)
Spencer, 2005 U.S. (Poor)	36/NR/110 26(25%) in MPH; 10(24%) in placebo dropout	Methylphenidate vs placebo, CGI rated "much" or "very much" improved: 63(68%) vs 6(17%), p<0.001

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Schubiner, 2002 U.S. (Fair)	Side effects checklist based on Barkley's (1990) version with the addition of cardiac symptoms	MPH vs placebo (*differences NS unless otherwise specified*) (*% worst occurrence during study*) Chest pain=0 vs 2 (8%) Palpitations=0 vs 1 (4%) Dizzy=2 (8%) vs 1 (4%) Stomachaches=3 (13%) vs 3 (13%) Nightmares=5 (21%) vs 3 (13%) Headaches=6 (25%) vs 6 (25%) Nausea or upset stomach=8 (33%) vs 5 (21%) Euphoria, unusually happy=10 (42%) vs 7 (29%) Drowsiness=6 (25%) vs 10 (42%) Tics or nervous movement=5 (17%) vs 5 (21%) Decreased appetite=12 (50%) vs 6 (25%) Insomnia or trouble sleeping=15 (63%) vs 8 (33%); p<0.05 Irritability=14 (58%) vs 13 (54%) Sadness=15 (63%) vs 9 (38%) Talk less with others=11 (46%) vs 12 (50%)	Methylphenidate vs placebo: Total withdrawals: 13 (54.2%) vs 10 (41.7%) Withdrawals due to adverse events: 0 vs 1 (4.2%)
Spencer, 1995 U.S. (Fair)	Elicited by investigator; HAM-D, HAM-A, BDI	Loss of appetite 26% Insomnia 22% Anxiety 22% Methylphenidate vs placebo: Mean heart rate 80 vs 76 beats/min (p<0.05) Mean weight 73.2 vs 74.3 kg (p<0.05)	Methylphenidate vs placebo, Total withdrawals 2 (8%) vs 0%; Withdrawals due to AEs: 2 (8%, chest pain in 1, agitation/irritability in another) vs 0%
Spencer, 2005 U.S. (Poor)	self-report	Methylphenidate vs placebo, Life events: 2(2%) vs 0(0%), p=0.37 Psychiatric adverse events: 7(7%) vs 0(0%), p=0.085 Somatic complaints: 2(2%) vs 0(0%), p=0.37	Methylphenidate vs placebo, Total withdrawals 26 (25%) vs 10(24%); Withdrawals due to AEs: 11(11%) vs 0(0%)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Schubiner, 2002 U.S. (Fair)	Comorbid for cocaine dependence Pemoline arm dropped (n=11) due to low enrollment after 1 year
Spencer, 1995 U.S. (Fair)	Outcomes from the first phase of treatment (MPH vs placebo) are presented separately, but number of patients in each group is not reported.
Spencer, 2005 U.S. (Poor)	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Tenenbaum, 2002 U.S. (Fair)	DB RCT crossover design	Participants were recruited via newspaper ads, outpatient therapy practices, support groups, and posted notices. Respondents with symptoms of ADHD, defined as either: (i) two of the primary subscales of the ADSA (both Attention-Focus/Concentration Scale and Behavior-Diagnosed Activity Scale) or (ii) both of the subscales of Barkley's ADHD Rating Scale (inattention and hyperactivity/impulsivity). ADSA ratings were significant when subscale scores were >=1.5 standard deviations above the mean. Ratings on Barkley's scale were significant according to age/gender normative scores per by Barkley & Murphy 1998. Diagnosis of ADD, combined type was determined using DSM-IV criteria, clinical interviews and standard rating scales. A significant other attended each of 3 assessment/baseline sessions to provide collateral information.	All study medications were administered quid, at morning, noon, 4PM and evening. Methylphenidate (up to 45 mg/day) dosed as follows, with placebo given at evening dose: Day 1-2: 5 mg AM and 5 mg noon, placebo 4PM Day 3-4: 5 mg AM, 5 mg noon, 5 mg 4PM Day 5-7: 10 mg AM, 10 mg Noon, 5 mg 4PM Day 8-10: 10 mg AM, 10 mg Noon, 10 mg 4PM Day 11-13: 15 mg AM, 15 mg noon, 10 mg 4PM Day 14-21: 15 mg AM, 15 mg noon, 15 mg 4PM Pycnogenol was administered qid, to a total dosage of 1 mg/lb body weight. Placebo qid Duration of each treatment phase: 3 weeks Duration of total trial: 17 weeks, including 1 week baseline phase, washout periods between treatment phases, and 3-week follow-up	Run-in NR; 1-week washout between treatment phases	NR
Turner, 2005	DB PCT crossover	Adult patient with ADHD who scored≥172 on the attention-deficit scales for adults (ADSA) and who also were assessed with the Global Severity Index (GSI)	Methylphenidate 30 mg single dose and placebo. Dose given 75 minutes before testing started.	NR / 12-hour washout for alcohol or caffeine	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Tenenbaum, 2002 U.S. (Fair)	Self-report rating scales, rating scales completed by the individual's significant other, and a computerized continuous performance test, conducted at baseline and end of each 3-week treatment hase, as well as 1 month after the final treatment condition. Self-reported rating scales: Barkley's ADHD rating scale, Attention Deficit Scales for Adults, Copeland Symptom Checklist for Adult Attention Deficit Disorders, Barratt Impulsiveness Scale, Conners' CPT, Brown ADD scales Other-reported data: Barkley's ADHD Scale, Attention Deficit Scales for Adults, Copeland Symptom Checklist for Adult ADD, Brown ADD Scales Composite scores for each scale were calculated as follows: the mean baseline score was subtracted from each subject's score at the end of each 3-week treatment phase, divided by standard deviation at baseline for the entire sample. For each research instrument the standardized scores for the subscales were then summed to provide one composite score for each participant for each treatment condition.	Mean age 42 45.8% male 100% white	Not reported	128/85/33 Same subjects exposed to all treatments.
Turner, 2005	Patients completed a Visual Analogue Scale (Bond and Lader 1974) that measured their feelings in terms of 16 dimensions before administration of the drug and on completion of testing. Patients were tested using the computerized Cambridge Neuropsychological Test Automated Batter (CANTAB) for Patter Recognition Memory (PRM), Spatial Working Memory (SWM), Spatial Span (SSP) and Rapid Visual Information Processing (RVIP). Testing sessions were separated by at least a week and lasted approximately 1 hour.	Mean age (for n=18 patients with DSM-IV ADHD): 28.5 70.4% male (of original 27 patients; no data specified for smaller group)	Mean baseline GSI =1.4 (SD:0.6) 18 of 24 patients met DSM-IV criteria for ADHD; 5 of these had a diagnosis of "inattentive type" and 7 of "combined type". 6 of 24 patients did not meet DSM-IV ADHD criteria; they were classified as patients with "attentional difficulties" and were not included in the main analysis of the effects of MPH .	NR / 27/ 27 same subjects exposed to both treatments

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results
Tenenbaum, 2002 U.S. (Fair)	9 (27%) withdrawn due to non-compliance 0% lost to fu 24 (72.7%) analyzed, N per drug not reported (phases were combined in analysis).	Composite score effect size, self-reported data; other-reported data: Barkley's ADHD Rating Scale 0.18/ 0.13; Attention Deficit Scales for Adults 0.19/0.09 Copeland Checklist for Adult ADD 0.20/0.23; Barratt Impulsiveness Scale 0.25/other na Conners' CPT 0.13/other na; Brown ADD Scales 0.25/0.22 Mean change from baseline in MPH vs placebo [Cohen's d effect size] from self-reported data; from other-reported data: Barkley's Inattention -2.75 v -2.79 [-.02] ; -1.18 v -1.57 [-.15] Barkley's hyperactivity -1.79 v -1.79 [.00] ; -.96 v -1.35 [-.17] ADS Attention-Focus -7.10 v -4.80 [.33] ; -2.50 v -3.50 [-.16] ADS Behavior-Disorganized Activity -9.00 v -7.80 [.13] ; -6.60 v -5.80 [.08] ADS Emotive Scale -4.90 v -5.10 [-.04] ; -3.50 v -3.00 [.07] Copeland Inattention/Distractibility -15.10 v -9.40 [.30] ; -1.90 v -8.20 [-.40] Copeland Impulsivity Scale -15.00 v -11.20 [.21] ; -5.10 v -7.80 [-.12] Copeland Overactivity/Hyperactivity -8.40 v -16.50 [-.42] ; -3.60 v -7.90 [-.20] Copeland Underactivity -12.50 v -8.20 [.22] ; -4.80 v -5.20 [-.03] Barratt Total scale -5.60 v -6.00 [-.04] ; Other-reported data n/a Barratt Cognitive impulsliveness scale -1.70 v -1.40 [.10] ; Other-reported data n/a Barratt motor impulsiveness -3.00 v -2.70 [.07] ; Other-reported data n/a Barratt non-planning impulsivity -.90 v -2.00 [-.22] ; Other-reported data n/a CPT: Standard Error of Hit Rate -1.27 v -1.25 [.01] ; Other-reported data n/a CPT: SE of variability in reaction times -.30 v -1.89 [-.40] ; Other-reported data n/a CPT: Hit rate minus interstimulus interv -.01 v -.01 [.10] ; Other-reported data n/a CPT: Intertrial interval -.01 v -.01 [-.02] ; Other-reported data n/a Brown total score -15.60 v -15.10 [.02] ; -12.80 v -18.80 [-.35] Brown: Activating and organizing to work -3.60 v -3.30 [.05] ; -3.80 v -3.80 [-.15] Brown: Sustaining attention and concentr -3.90 v -3.30 [.13] ; -2.70 v -4.70 [-.34] Brown: Sustaining effort and energy -3.60 v -3.20 [.07] ; -2.70 v -3.80 [-.21] Brown: Managing affective interference -2.13 v -2.67 [-.14] ; -1.80 v -2.30 [-.13] Brown: Utilizing working memory and reca -2.30 v -2.70 [-.09] ; -2.00 v -3.30 [-.41] Beck Depression -1.68 v -3.68 [-.31] ; Other-reported data n/a Beck Anxiety .12 v -2.17 [-.54] ; Other-reported data n/a Avg.effect size [-.02] ; [-.18]
Turner, 2005	3 / NR / 24 (24 per drug)	No significant differences were seen between placebo and methylphenidate for the PRM, and the SSP, and none were seen for 3 of 4 parts of the SWM and for 1 of 3 parts of the RVIP. For the significant differences on the SWM, methylphenidate vs placebo: Between errors 6-box stage scores (SD) were: 2.3 (3.1) vs 6.8 (6.7), p = 0.0026 For the significant differences on the RVIP, methylphenidate vs placebo: Mean latency in milliseconds: 416.5 (67.7) vs 468.3 (85.1), p=0.006 Target sensitivity scores: 0.931 (0.006) vs 0.908 (0.06), p=0.026 On the VAS assessing patient's feelings, of the 16 different domains, the increases between methylphenidate vs placebo on these 7 feelings were significant: Alert, well-coordinated, contented, tranquil, quick-witted, attentive, interested

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Tenenbaum, 2002 U.S. (Fair)	NR	NR	Methylphenidate vs placebo: Total withdrawals unclear by treatment group. Withdrawals due to AEs 0 vs 0
Turner, 2005	NR	NR	3 enrolled patients did not have complete data, but no information was given about these patients.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Tenenbaum, 2002 U.S. (Fair)	Data from the first treatment phase was not reported separately. The effect sizes in the composite scores ANOVAs were uniformly small (0.09-0.25), accounting for no more than 6% of the variance, indicating that treatment effects of MPH and Pycnogenol were not superior to those of placebo. Most of the effect sizes for all measures comparing MPH with placebo were very small and mostly negative. Only 3 of the 80 effect sizes reached the criterion of 0.50 for a moderate effect size, and in each of these cases the effect size was negative. These results show that MPH and pycnogenol were no better, and perhaps even slightly worse, than placebo.
Turner, 2005	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Wender, 1985 U.S. (Fair)	DB RCT crossover design	Clinics were asked to refer white patients aged 21-45 with prominent complaints of impulsivity, irritability restlessness, and emotional lability. Included patients whose mothers were available and willing to fill out the Parent Rating Scale, with IQ >90. Patients were interviewed with a semistructured personal and family history instrument. Utah criteria for ADD, residual type; subject must first have had a history of ADHD in childhood as well as both hyperactivity and ADD persisting from childhood, and additionally have affective lability; inability to complete tasks; hot or explosive temper; impulsivity; and stress intolerance. Mothers of prospective patients rated the behavior of their offspring between ages 6 and 10, using a modified Conners Teacher's Rating Scale.	Methylphenidate or placebo were dispensed in 10-mg tablets. Initial dose was 5 mg bid, at 8AM and 12 noon, increased by 5 mg per dose every 2-3 days on the basis of patient's report. Maximum dose was set at 3 tablets tid (90 mg/day). Methylphenidate mean dose at end treatment phase 43.2 mg/day. Placebo mean dose at end treatment phase 50.2 mg/day Randomized crossover design with 1-week washout between 2-week treatment phases; total duration 5 weeks.	Run-in NR; 1-week washout between treatment phases	NR
Wood, 1976 (Fair)	DB, crossover design	Adults who had a rating, as children, of hyperactivity from parents's report (Conner Abbreviated Rating Scale) scoring over the 95th percentile, with prominent complaints of no change in adulthood.	Methyphenidate for 2 weeks twice daily, at variable, NR dose amounts, gradually increased to max of 60mg. Crossover: to methyphenidate, doses varying to 20-60 mg/day (specifics NR)of: Methylphenidate or Pemoline	Run-in NR. No washout given due to short duration of drug	Imipramine, 10mg, was used with 1 subject, who did not respond to Pemoline,
Carpentier 2005	DB RCT double cross-over in in-patients at openaddiction trmt facility	positive diagnosis of ADHD w/ 6 criteria from DSM IV	Day 1–3 1 tablet t.i.d. 15 mg Day 4–7 2 tablets t.i.d. 30 mg Day 8–14 3 tablets t.i.d. 45 mg and two weeks placebo repeated (so 4 rounds) Duration 8 weeks	Detoxification of 3 weeks if necessary	one patient on methadone
Methylphenidate SR					
Levin 2002 U.S. (Fair)	DB RCT parallel design	Adults ages 19-56; all were positive for ADHD according to DSM-IV; all were nonsmokers verified by endtidal carbon monoxide measurements less than 8 ppm; an experienced clinical psychologist made the diagnoses of ADHD using the Wender Utah Rating Scale, the Conners/Wells Adolescent and Adult Self-Report, a modified version of Barkley's adult ADHD semistructured interview	Placebo Nicotine transdermal patches: Week 1=5 mg per day, Weeks 2-3=10 mg per day, Week 4: 5 mg per day Methylphenidate sustained release 20 mg per day Nicotine+methylphenidate sustained release Duration: 4 weeks	NR/NR	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Wender, 1985 U.S. (Fair)	Clinical status was evaluated at beginning of each treatment phase, 1 week following initiation, and at end of 2-week drug or placebo phase. Physician's target symptom rating scale Physician's Global Rating Scale Medicine response sheet (self-rating instrument) Global Assessment Scale Profile of Mood States SCL-90	Mean age 31.1 54% male Ethnicity NR	Comorbidities: 68% dysthymic disorder 22% cyclothymic disorder	NR/NR/37 Same subjects exposed to both treatments
Wood, 1976 (Fair)	12 month assessment self-report of symptoms from patients, completion of self-report questionnaire	N=15 but only 11 in cross-over Age Range: 21-60 Ethnicity:Caucasian Male: 40% (of the 15 total)	RDC diagnoses: generalized anxiety disorder: n=8 cyclothymic disorder: n=4 drug/alcohol abuse: n=2 antisocial disorder: n=2 minor depressive disorder: n=4 N>15, as patients as patients over-lapped in these diagnoses	15/11 N per drug NR
Carpentier 2005	ADHD-RS Clinical Observation Scale Clinical Global Impression Scale Assessed at baseline and weekly	Mean age=31.9 88% male race nr	Type of substance abuse Alcohol 52.0% Drug 92%	NR/NR/25
Methylphenidate SR				
Levin 2002 U.S. (Fair)	CGI scale assessed by clinician on Treatment Days 1, 8 and 21 Individual questions from the Profile of Mood States (POMS) battery (tension, fatigue, vigor, depression, anger and difficulty concentrating: Treatment days 1, 8, 15 and 21 Conners CPT: Treatment days 1 and 21 Automated Neuropsychological Assessment Metrics (ANAM): simple reaction time, mental spatial rotation reaction time and delayed matching to sample administered on Treatment Days 1 and 21	Mean age=37 62.5% male race nr	NR	NR/NR/40 Placebo patch + placebo pill, n=10 Nicotine, n=10 Methylphenidate, n=10 Nicotine + methylphenidate, n=10

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results
Wender, 1985 U.S. (Fair)	0% withdrawn; 0% lost to followup; 37 (100%) analyzed, N per drug not reported (phases were combined in analysis).	Final physician and patient ratings, methylphenidate vs placebo: Physician's Global Rating scale 1.4 vs 0.16 (p<0.005) Global Assessment Scale 69.17 vs 61.26 (p<0.005) Physician's target symptom ratings (1=none, 4=marked): hyperactivity 2.33 vs 3.29 (p<0.005); short attention span 2.27 vs 3.35 (p<0.0005); mood problems 2.36 vs 3.14 (p<0.005); anger 2.35 vs 3.11 (p<0.01); disorganization 2.12 vs 3.03 (p<0.005); conduct disorder 1.42 vs 1.67 (ns) Patient's subjective experience (1=absent, 5=very much): nervous 2.56 vs 2.97 (ns); happy 3.16 vs 2.70 (p<0.05); energetic 3.27 vs 3.11 (ns); mind wandering 2.37 vs 2.97 (p<0.025); hot tempered 2.32 vs 2.43 (ns); calm 2.83 vs 2.35 (ns); sad 1.81 vs 2.10 (ns); tired/sleepy 1.88 vs 2.28 (ns); concentrating 2.86 vs 2.41 (ns); hungry 1.97 vs 2.51 (p<0.025); cool tempered 3.97 vs 2.44 (p<0.025); global 4.97 vs 4.31 (ns) Profile of mood states: tension-anxiety 49.06 vs 55.71 (p<0.001); depression-dejection 43.88 vs 50.50 (p<0.001); anger-hostility 50.34 vs 57.03 (p<0.01); vigor 70.40 vs 66.53 (ns); fatigue 48.00 vs 53.47 (p<0.05); confusion 51.53 vs 58.25 (p<0.001) BDI 8.94 vs 9.23 (ns)
Wood, 1976 (Fair)	0/0/11 analyzed: N NR	**Self-rating Responses of Double-Blind Trial (n=11) of Methyphenidate vs Placebo** Methylphenidate vs Placebo; p-Value Happy-Sad: 1.37 vs 2.66; pNS Calm-Nervous: 2.15 vs 3.60; p=.01 Energetic-Tired: 1.66 vs 3.25; p=.05 Concentrating Mind-Wandering Mind: 1.75 vs 3.28; p=.01 Cool-Tempered-Hot-Tempered: 1.65 vs 3.55; p=.01
Carpentier 2005	6/3/2019	Mean (SD) ADHD rating scale Placebo 31.8 (12.7) MPH 27.6 (15.3) (P = 0.352) Clinical Observation scale Placebo 17.8 (8.1) MPH 14.0 (9.2) (P = 0.211) Clinical Global Impression scale Placebo 8.3 (3.9) MPH 6.5 (4.3) (P = 0.184) Responders 30% reduction in in all 3 trmt scales Placebo 5 MPH 9
Methylphenidate SR		
Levin 2002 U.S. (Fair)	6 (15%) withdrawn/lost to fu nr/34 analyzed (placebo n=7, nicotine n=9, MPH n=9, combination n=9)	MPH vs placebo (differences are NS unless otherwise noted) CGI Day 1 (acute): 5.0 vs 4.8 Days 15 and 28 (chronic): 5.4 vs 4.1 Change from baseline to day 28: -0.5 vs -0.6 POMS MPH vs placebo on day 21: F(1,26)=6.55, p=0.025; NS on days 1, 15 and withdrawal days (data nr) CPT Omission-- Acute: 2.4 vs 1.0; Chronic: 1.0 vs 1.3 Commission errors-- Acute: 16.6 vs 13.0; Chronic: 12.2 vs 13.1 Reaction time (ms)-- Acute: 324 vs 355; Chronic: 326 vs 329 Reaction time variability-- Acute: 7.8 vs 7.7; Chronic: 6.0 vs 6.0 Attention-- Acute: 2.7 vs 3.4; Chronic: 3.5 vs 3.0 ANAM Reaction time (ms): 280 vs 293 Spatial rotation (ms): 2,208 vs 2,198 Delayed matching (%): 91.9 vs 91.2

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Wender, 1985 U.S. (Fair)	Self-report	Mild anxiety, insomnia, jaw tension, tooth grinding, overstimulation, irritability, nose tingling	Methylphenidate vs placebo: Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0
Wood, 1976 (Fair)	self-report, results on questionnaire data	No adverse effects reported, no response to meds: n=1	0/0
Carpentier 2005	NR	MPH showed significantly more side effects than placebo (F = 4.30, df = 1.87, P = 0.03).	Total withdrawals 6 1 withdrawal due to Aes on placebo
Methylphenidate SR			
Levin 2002 U.S. (Fair)	NR	NR	Methylphenidate vs placebo, Total withdrawals: 1 (10%) vs 3 (30%); p=NS Withdrawals due to adverse events nr

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Wender, 1985 U.S. (Fair)	Data from the first phase was not reported separately. Outcomes were presented as combined data from phases of each drug.
Wood, 1976 (Fair)	
Carpentier 2005	
Methylphenidate SR	
Levin 2002 U.S. (Fair)	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Biederman 2006	DB RCT parallel design	Outpatients 19–60 years. To be included, subjects had to satisfy full diagnostic criteria for DSM-IV ADHD on the basis of clinical assessment and confirmation by structured diagnostic interview	Osmotic release oral system methylphenidate (OROS MPH) vs. placebo titrated to optimal response (a maximum daily dose of 1.3 mg/kg; initial dose of 36 mg 6 weeks	NR	No
Reimherr 2007	DB RCT crossover design	Adults (18-65 yrs) with current diagnosis of ADHD using DSM-IV with at least moderate symptoms	Osmotic release oral system methylphenidate (OROS MPH) vs. placebo, titrated up from 18 mg per day until response w/ maximum dose of 90 mg per day. 2 arms 4 weeks each	No	NR
Levin 2006 U.S.	DB RCT	Ages 18-60, meet DSM-IV criteria for opiate dependence and adult ADHD, on the same dose of methadone for at least 3 weeks	Placebo, sustained-release MPH, and sustained-release bupropion (BPR) 2-week placebo lead-in, 2-week dose titration period followed by 8 weeks at stable dose MPH titration phase standard formulation 2X/day starting at 10 mg/day increased by 10 mg/day, up to 40 mg/day, then standard formulation replaced by sustained-release formulation as two 20 mg doses, dose increased up to maximum of 80 mg/day. Patients discontinued if could not tolerate at least 40 mg/day MPH. BPR was started at 100 mg/day and increased by 100 mg by the end of the first week of the titration phase. Patients received 200 mg 2 X/day for the maximum dose of 400 mg/day by the end of the second week. Patients discontinued if could not tolerate at least 200 mg/day BPR.	Two week placebo lead-in	Medication and treatment at a methadone program, weekly individual cognitive behavioral therapy for drug use
Levin 2007 U.S.	DB RCT	ages of 18–60 to meet DSM-IV criteria for cocaine dependence and persistent adult attention deficit hyperactivity disorder	Placebo and MPH dosing was initiated at 10 mg/day of standard formulation methylphenidate and increased up to 20 mg two times a day (40 mg/day) one week lead-in, two week titration and 11 weeks at stable dose	One week placebo lead-in	Not reported (NR)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Biederman 2006	CGI-I CGI-S Adult ADHD Investigator System Report Scale score. Assessed baseline, weekly and endpoint	Placebo/OROS MPH Age 37.6/32.7 Male 47%/57% Ethnicity NR	Placebo/OROS MPH CGI Severity Mild 0/1 Moderate 56/40 Marked 29/38 Severe 3/1 P = 0.1 Lifetime Psychiatric Comorbidity 46% / 33% P = 0.1	204/276/149 - Placebo 77 OROS MPH 72
Reimherr 2007	Wender-Reimherradult ADD Scale ADHD-RS CGI-I Assessed weekly	Age 30.6 Male 66% Ethnicity NR	#(%) ADHD alone 8(17) ADHD + Emotional dysregulation 18(38) ADHD +ED+ODD 19(40)	NR/NR/47
Levin 2006 U.S.	Weekly clinical assessments of ADHD symptoms using: AARS as primary measure Clinical Global Improvement Scale (CGI) Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS)	Mean age placebo/MPH/BPR 39/40/38, p=0.59 57% male 40% white 40% Hispanic 20% black	Currently employed at baseline placebo/MPH/BPR 43%, 58%, 89%, p=0.001 34% enrolled in methadone maintenance program for less than 12 weeks, 58% enrolled for more than 6 months	526/232/115 33 placebo 32 MPH 33 BPR
Levin 2007 U.S.	AARS Clinical Global Improvement scale (CGI) Targeted Adult Attention Deficit Disorder Scale (TAADDS)	Mean age 37.0 83% male 60% white 20% black 14% Hispanic 6% other	Employed full-time 72% placebo 50% MPH Baseline AARS Placebo 33.47 MPH 30.40	1125/580/124 Placebo 53 MPH 53

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results
Biederman 2006	Placebo/MPH Withdrawn 11/18 Lost to F/U 4/7 Analyzed 74/67	Response of much or very much improved on the Clinical Global Impression–Improvement scale plus a >30% reduction in Adult ADHD Investigator System Report Scale score Placebo 39% vs. OROS MPH 66% P = NR
Reimherr 2007	6/NR/43-safety 41-efficacy	Mean total WRAADS score decrease Placebo 13% vs 42% OROS MPH P < 0.001 Mean total ADHD-RS score decrease Placebo 14% vs 41% OROS MPH P = 0.003
Levin 2006 U.S.	Placebo/MPH/BPR Withdrawn 8/11/10 Lost to F/U NR Analyzed 25/21/23	AARS response >30% reduction placebo 46%, MPH 34%, BPR 49%, p=0.48 CGI response improvement rating <3 placebo 39%, PMH 19%, BPR 30%, p=0.19 No significant differences in any drug or cocaine use.
Levin 2007 U.S.	Placebo/MPH Withdrawn 29/30 Lost to F/U NR	AARS response rate 30% reduction Placebo 55% MPH 47% P = 0.44 Clinical Global Improvement scale (CGI) Placebo 30% MPH 34% P = 0.68 Targeted Adult Attention Deficit Disorder Scale (TAADDS) response 30% reduction Placebo 40% MPH 28% P = 0.22 No significant differences in cocaine use

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Biederman 2006	Spontaneous reports through open-ended questions at each visit. Weight and vital signs were obtained at each visit, and an ECG was performed at baseline and endpoint.	OROS MPH / Placebo n(%) Decreased Appetite (Anorexia) 23 (34) / 2 (3) , P < .001 Dry Eyes, Nose, Mouth 23 (34) / 5 (7) P < .001 Headache 21 (31) / 22 (30) P = .8 Gastrointestinal 19 (28) / 10 (14) P = .03 Colds/Allergies/Infections 12 (18) / 18 (24) , P = .4 Tension/Jitteriness 12 (18) / 0 (0) , P < .001 Sleep Problems 12 (18) / 4 (5) , P = .02 Aches/Pains 9 (13) / 10 (14) , P = .9 Cardiovascular Complaints 6 (9) / 1 (1) , P = .04 Depression 5 (8) / 0 (0) , P = .02 Agitation 5 (7) / 6 (8) , P = .9 Dizziness 5 (7) / 0 (0) , P = .02 Menstrual Problems 2 (7) / 0 (0) , P = .1 Anxiety 4 (6) / 0 (0) , P = .03 Change in Systolic BP 3.5 vs. -1.1 P = 0.02 Diastolic BP 4.0 vs. -2.1 P < 0.001 Heart rate (bpm) 4.5 vs. -2.7 P < 0.001 QTC interval (msec) 1.9 vs. -1.2 P = 0.3	Placebo/MPH Total 11/18 Due to Aes (side effects) 3/9
Reimherr 2007	Assessed at interviews and spontaneously reported	Placebo/ OROS MPH Mean weight change lbs 1.3 / -2.5 Decreased appetite 0/5 Sleep/insomnia 3/9 Anxiety 0/4 Subjects w/ at least 1 AE 39% / 55% at moderate impairment 23% / 39%	By trmt NA Total withdrawals 6 due to Aes NR
Levin 2006 U.S.	NR but rated on a 0 to 3 scale (none to severe)	Fatigue 9% placebo Increased sweating MPH 6%, BPR 9% Nosebleed placebo n=1 Psychomotor agitation MPH n=1	Placebo/MPH/BPR Total withdrawn 8/11/10 Withdrawn AEs (side effects) 2/1/0
Levin 2007 U.S.	NR but rated on a 0 to 3 scale (none to severe)	Headache placebo 2% MPH 8% GI upset placebo 4% MPH 8% Diarrhea placebo 9% MPH 2% Insomnia placebo 2% MPH 9%	Placebo/MPH Total 29/30 Due to Aes (side effects) 1/1 Most withdrew because "Not interested" 22/19

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Biederman 2006	
Reimherr 2007	
Levin 2006 U.S.	
Levin 2007 U.S.	

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Study Design Setting	Eligibility criteria	Interventions (drug, regimen, duration)	Run-in/ Washout period	Allowed other medications/ interventions
Mixed amphetamine salts Extended Release					
Weisler 2006	DB RCT	outpatients >18 years of age who were referred by clinics and had a primary diagnosis of ADHD established by psychiatric evaluation using *DSM-IV-TR* criteria	Daily morning dose of placebo MAS XR 20 mg, 40 mg, or 60 mg for 4 weeks	One week washout	NR
Modafinil					
Turner, 2004 U.K. (Fair)	DB RCT crossover design	DSM-IV diagnosis of ADHD; DSM-IV ratings from patient and/or informant of predominantly inattentive type and/or hyperactive-impulsive type during childhood and previous 6 months, and judgment by a consultant psychiatrist that patients' symptoms interfered with ability to function and were not explained by another disorder. Patients were also assessed by the GSI.	Modafinil single oral dose of 200 mg Lactose placebo, single oral dose 10 subjects were randomized to receive a single oral dose of lactose placebo first, followed by single dose of modafinil in the second session; the time of day that the dose was administered was not reported. 10 subjects were randomized to receive the drug first, followed by placebo. The single-dose treatment sessions were separated by one week. Duration: 1 week	Run-in NR; 1-week washout between single-dose treatment phases	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled N per drug
Mixed amphetamine sa				
Weisler 2006	ADHD rating scale at clinic visits Conners' Adult ADHD Rating Scale-Short Version-Self-Report (CAARS-S-S) 4- and 12-hours postdose 3 days/week during the washout week and each of the 4 treatment weeks. CGI-S baseline and endpoint CGI-I baseline and weekly CGI-E weekly	Mean age (yrs): Placebo 39.3 20mg 38.8 40mg 38.9 60mg 39.9 Male (%) Placebo 68 20mg 64 40mg 59 60mg 48 Ethnicity (%) White: Placebo 90 20mg 87 40mg 91 60mg 88 African American: Placebo 5 20mg 5 40mg 3 60mg 0 Hispanic: Placebo 3 20mg 6 40mg 3 60mg 8 Other: Placebo 2 20mg 2 40mg 3 60mg 3	Years since diagnosis Placebo 5.0 20mg 4.6 40mg 4.9 60mg 7.1 ADHD-RS (baseline) Placebo 33.0 20mg 31.1 40mg 31.3 60mg 32.9	339/259/255 Placebo-64 20mg-66 40mg-64 60mg-61
Modafinil				
Turner, 2004 U.K. (Fair)	Patients were tested 2 hours post drug administration for approximately 2 hours. Testing sessions were separated by at least a week. Neuropsychological test battery, including CANTAB; Logan stop-signal task; PRM task; IDED; NTOL The order in which patients received the tasks differed for placebo and drug conditions and was randomized across patients.	Mean age 28 65% male Ethnicity NR	Mean NART score 108 Mean GSI score 1.6 Mean education 13.5 Subjects were matched for age, NART verbal IQ, education level, and GSI, previous use of stimulant medication, current use of stimulant medication	NR/NR/20 Enrolled in 1st treatment phase: 10 in modafinil, 10 in placebo

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Number withdrawn/ lost to fu/ analyzed: N per drug	Results
Mixed amphetamine sa		
Weisler 2006	Number withdrawn Placebo 22 20mg 19 40mg 15 60mg 16 Lost to FU Placebo 2 20mg 4 40mg 1 60mg 3 Analyzed Placebo 60 20mg 64 40mg 64 60mg 60	**ADHD-RS Placebo adjusted difference (95% CI)** 20mg -6.6 (-11.0 to -2.3) 40mg -7.2 (-11.5 to -2.8) 60mg -7.8 (-12.2 to -3.4) **CGI-I (much or very much improved)** Placebo 27% MAS XR 55% CGI-E ("marked—vast improvement" or "moderate—decided improvement") Placebo 25% 20mg 56% 40mg 59% 60mg 60% **CAAR-S-S ADHD Index 12 hours postdose** placebo-adjusted difference (95% CI) 20mg -3.31 (-5.6 to -1.1) 40mg -3.2 (-5.4 to -0.9) 60mg -4.9 (-7.1 to -2.6)
Modafinil		
Turner, 2004 U.K. (Fair)	Withdrawn NR Lost to followup NR 20 (100%) analyzed Analysis of 1st treatment phase included 10 in modafinil, 10 in placebo	Mean score among outcomes with significant drug x order interactions, on which a between-subjects analysis for the first session only was performed, modafinil vs placebo: Immediate PRM % correct 91.25 vs 91.25 (ns) DMTS % correct 87.50 vs 79.80 (p=0.016) SSP span length 6.50 vs 6.35 (ns); total errors 53.65 vs 55.10 (ns) NTOL latency (all moves) 19126 vs 15351 ms (p=0.004) RVIP target sensitivity (A') 0.937 vs 0.926 (ns) Mean scores on other tests, on which data from both sessions was combined, modafinil vs placebo: Digit span forwards score: 9.45 vs 8.00 (p<0.001); backwards score 8.35 vs 7.00 (p=0.017) Immediate PRM response latency 1889 vs 1714 ms (ns) Delayed PRM % correct 8735 vs 79.8 (p=0.016); response latency in ms 2340 vs 1769 (ns) PAL 1st trial memory score 16.7 vs 15.8 (ns); total errors 9.25 vs 9.95 (ns); total trials 8.1 vs 8.65 (ns) DMTS latency 5057 vs 4121 ms (ns) SWM strategy score 29.5 vs 30.1 (ns); between errors 17.35 vs 19.8 (ns); within errors 1.3 vs 1.35 (ns) NTOL mean attempts (all moves) 7.22 vs 7.86 (p=0.009) RVIP mean latency 439 vs 434 ms (ns); response bias (B") 0.83 vs 0.97 (ns) IDED total errors 24.4 vs 22.4 (ns); total reversal errors 12.2 vs 12.9 (ns); total EDS errors 7.7 vs 4.9 (ns) Gamble probability of choosing most likely outcome 0.92 vs 0.91 (ns); % bet (average) 58.7 vs 57.44 (ns); deliberation time 2473 vs 2244 ms (ns) STOP go reaction time 444 vs 420 ms (ns); go reaction time variability 137 vs 124 (ns); stop-signal reaction time 150.1 vs 172.7 (p=0.028); errors 5.7 vs 3.0 (ns)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	By treatment, total withdrawals; withdrawals due to adverse events
Mixed amphetamine sa			
Weisler 2006	Physical examination, neurologic evaluation, vital sign measurements, and clinical laboratory test results. A 12-lead ECG, performed at baseline and 2-week intervals,	Placebo/20mg/40mg/60mg (%) Anorexia: 3/20/42/38 Insomnia: 13/21/30/26 Headache: 16% vs 4% (p=0.18)3/14/30/26 Nervousness: 13/11/16/12 Dry mouth: 5/24/44/38 Weight loss: 0/5/16/12 Nausea: 5/8/6/10 Agitation: 5/8/6/10 Anxiety: 3/6/6/10	Total withdrawals Placebo 22 20mg 19 40mg 15 60mg 16 Withdrawals due to Aes (%) Placebo 1 20mg 9 40mg 6 60mg 8
Modafinil			
Turner, 2004 U.K. (Fair)	Subjective measures were self-rated on 16 measures. Blood pressure and pulse were taken before drug administration and at 2, 3, and 4 hours after drug administration.	NR	Modafinil vs placebo, Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Comments
Mixed amphetamine sa	
Weisler 2006	
Modafinil	
Turner, 2004 U.K. (Fair)	

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity						
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Biederman, 2006	Method NR	Method NR	No, SS difference in age and ADHD onset	Yes	NR	NR	Yes
Bouffard, 2003	No (numbers chosen from a hat)	No (see comment in Evidence Table)	Not reported by phase; same subjects exposed to both treatments	Yes	Yes but method not described	NR	Yes but method not described
Carpentier, 2005	Method NR	Method NR	NR	Yes	NR	NR	Yes
Cox, 2000	Method NR	Method NR	Yes, except for history of moving violations and car crashes	Yes	Yes	Yes	Yes
Gualtieri, 1985	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes but method not described	NR	Yes but method not described
Kinsbourne, 2001	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes	NR	Yes
Levin, 2001	NR	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	*Internal Validity* Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis; If No: % analyzed	Post-randomization exclusions	Quality rating
Biederman, 2006	NR NR NR NR	No/ no	No 141/149 (95%) analyzed	No	Poor
Bouffard, 2003	Yes NR NR NR	No/ no	No: 79%	No	Fair
Carpentier, 2005	NR NR NR NR	No/ no	No 19/25 (76%) analyzed	No	Fair
Cox, 2000	Yes NR NR NR	No/ no	Yes	No	Fair
Gualtieri, 1985	NR NR NR NR	No/ no	Yes	No	Fair
Kinsbourne, 2001	Yes NR NR NR	No/ no	Yes	No	Fair
Levin, 2001	Yes NR NR NR	NR	No	No	Fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	*External Validity* Number screened/ eligible/ enrolled	Exclusion criteria
Biederman, 2006	204/178/149	Clinically significant chronic medical conditions, abnormal baseline laboratory values, IQ <80, delirium, dementia, amnesic disorders, other clinically unstable psychiatric condition; drug or alcohol abuse or dependence w/in 6 mos; previous participation in MPH trial
Bouffard, 2003	93/NR/38 Same subjects exposed to both treatments	Excluded psychiatric conditions that better accounted for their current symptoms or required other treatment; substance abuse in preceding 6 months; medical condition contraindicating stimulants (that is, hypertension or cardiac disease)
Carpentier, 2005	NR/NR/25	Psychiatric comorbidity that prevented study protocol compliance
Cox, 2000	NR/NR/13 Same subjects exposed to both treatments	Excluded major psychiatric illness and Tourette's disease (screened using SCID), and active (past 12 month) substance abuse using the Michigan Alcoholism Screening Test and a urine drug screen.
Gualtieri, 1985	NR/NR/8 Same subjects exposed to both treatments	Not reported
Kinsbourne, 2001	NR/NR/17 Same subjects exposed to all treatments	Not reported
Levin, 2001	NR/NR/40 Placebo patch + placebo pill, n=10 Nicotine, n=10 Methylphenidate, n=10 Nicotine + methylphenidate, n=10	Participants with diagnoses of major depressive disorder or generalized anxiety disorder were excluded; medical exclusion criteria covered all relevant concerns for use of nicotine in a transdermal patch form: hypertension, cardiac disease, cerebrovascular disease, impaired renal function, history of seizure, skin disease, sensitivity to medical dressings or tapes, and history of skin allergies

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

External Validity

Author, Year	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Biederman, 2006	NR/NR	No	Yes	McNeil Consumer and Specialty Pharmaceuticals	Yes
Bouffard, 2003	3-day run-in of increasing dosages (15/30/45 mg/day); 5 to 7-day washout btw. active & placebo phases	No	Yes	FRSQ grant	Yes
Carpentier, 2005	Washout of psychotropic medication (duration NR)	NR	Yes	Novadic-Kentron Institute	Inpatients
Cox, 2000	NR/NR	No	Yes	University of Virginia Health Sciences Center grant	Yes
Gualtieri, 1985	Run-in NR; 68-hr washout between treatment phases	No	Yes	USPHS Grant HD-10570	Yes
Kinsbourne, 2001	NR/NR	No	Yes	Not reported	Yes
Levin, 2001	NR/NR	Unclear	Yes	NR	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity						
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Levin, 2006	Method NR	Method NR	Yes, except for employment status (significantly higher proportion of pts in bupropion group employed)	Yes	NR	NR	Yes
Levin, 2007	Method NR	Method NR	Yes	Yes	NR	NR	Yes
Mattes, 1984	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes but method not described	NR	Yes but method not described
Michelson, 2003	Yes	Method NR	Yes	Yes	Yes	NR	Yes
Paterson, 1999	Method NR	Method NR	Yes	Yes	Yes but method not described	NR	Yes
Reimherr, 2007	Method NR	Method NR	Yes - there were some difference b/t groups but they did not reach statistical significance	Yes	NR	NR	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	*Internal Validity* Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis; If No: % analyzed	Post-randomization exclusions	Quality rating
Levin, 2006	NR NR NR NR	No/ no	Yes	No	Fair
Levin, 2007	NR NR NR NR	No/ no	Yes	No	Fair
Mattes, 1984	Yes NR NR NR	No/ no	No: 92%	No	Fair
Michelson, 2003	Yes NR NR NR	No/ no	No: 96%	No	Fair
Paterson, 1999	Yes Yes Yes Yes	No/ no	Yes	No	Fair
Reimherr, 2007	NR NR NR NR	No/ no	No Efficacy analysis: 41/47 (87%) Safety analysis: 43/47 (91%)	No	Fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	*External Validity* Number screened/ eligible/ enrolled	Exclusion criteria
Levin, 2006	526/232/98	DSM-IV criteria for current psychiatric disorders other than ADHD or substance abuse; physiologically dependent on sedatives or alcohol; suicidal or homicidal behavior within 2 yrs of study; use of prescription psychotropic medications other than methadone; unstable medical condition that would make participation hazardous; known sensitivity to methylphenidate or bupropion; nursing and/or pregnant; could not read or understant self-report assessment forms unaided or so severly impaired they could not comply with the requirements of the study
Levin, 2007	1,125/580/106	DSM-IV criteria for current psychiatric disorders other than ADHD or substance abuse; physiologically dependent on opiods, sedatives or alcohol; suicidal or homicidal behavior within 4 yrs of study; use of prescription psychotropic medications other than methadone; unstable medical condition that would make participation hazardous; known sensitivity to methylphenidate; nursing and/or pregnant; unable to give full and informed consent
Mattes, 1984	2829/116/66 Same subjects exposed to both treatments	Excluded patients who met DSM-III criteria for schizophrenia, major affective disorder except a major depressive episode of mild severity, any other psychosis, mental retardation (mild or worse), organic brain syndrome, or current drug or alcohol dependence (drug or alcohol abuse was allowed).
Michelson, 2003	448/329/280 Atomoxetine n=141 Placebo n=139 388/325/256 Atomoxetine n=129 Placebo n=127	Excluded patients with current major depression or anxiety disorder; patients with current or past bipolar or psychotic disorders; patients with serious medical illness; patients who met DSM-IV criteria for alcohol dependence. Patients actively using recreational drugs at time of study entry were excluded. Urine screening for drugs of abuse was performed at the initial visit, and could be repeated during the trial at the investigator's discretion.
Paterson, 1999	68/51/45 24 dexamphetamine 21 placebo	Patients were excluded if they had an insufficient ADHD score, or comorbidity for other major psychiatric disorders, including a history of current substance abuse. Organic disorders that would contraindicate the use of dexamphetamine were also excluded.
Reimherr, 2007	NR/NR/41	DSM-IV current at time of study diagnosis of major depressive disorder, generalized anxiety disorder, panic disorder, OCD, PTSD, bipolar disorder, schizophrenia, other psychotic disorder; seizure disorder, hyper- or hypothyroidism; medical conditions likely to be destabilized with MPH treatment

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity				
Author, Year	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Relevance**
Levin, 2006	2 wk placebo run-in; washout NR	No	Yes	NIDA grants #R01 DA00144, K02 00465 and K02 DA 00288	Yes
Levin, 2007	1 wk placebo run-in, washout NR	No	Yes	NIDA grants # ROI DA11755 and K02 00465	Yes
Mattes, 1984	NR/NR	No	Yes	Public Health Service grant	This study included adults with ADD symptoms, with or without ADHD in childhood. Outcomes represent 26 patients with childhood ADHD; AEs reflect the experience of all study subjects.
Michelson, 2003	1-week washout, followed by 2-week placebo lead-in phase	No	Yes	Eli Lilly	Yes
Paterson, 1999	NR/NR	No	Yes	Health Department of Western Australia	Yes
Reimherr, 2007	Screening/baseline run-in (not further described)	NR	Yes	McNeil Pediatrics	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity						
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Schubiner, 2002	NR	NR	No; MPH>placebo in ASI psychiatric composite scores	Yes	Yes	Yes	Yes
Spencer, 1995	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes	NR	Yes
Spencer, 2001	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes	NR	Yes
Spencer, 2005	Method NR	Method NR	No - MPH group younger	Yes	Yes	Yes	Yes
Spencer, 1998	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	NR	NR	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	*Internal Validity* Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis; If No: % analyzed	Post-randomization exclusions	Quality rating
Schubiner, 2002	Yes NR NR NR	NR	Yes	No	Fair
Spencer, 1995	Yes NR NR NR	No/ no	No: 92%	No	Fair
Spencer, 2001	Yes NR NR NR	No/ no	No: 90%	No	Fair
Spencer, 2005	Yes NR NR NR	NR	No	No	Poor
Spencer, 1998	Yes NR NR NR	No/ no	No: 95.4%	No	Fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	*External Validity* Number screened/ eligible/ enrolled	Exclusion criteria
Schubiner, 2002	932/338/59 Methylphenidate n=24 Placebo n=24 Pemoline n=11 (dropped from analysis)	Less than an estimated IQ of 75 on the Shipley Institute of Living scale; schizophrenia, bipolar disorder, dementia, and delirium
Spencer, 1995	85/25/25 N per drug during first phase not reported.	Excluded prospective subjects if they had any clinically significant chronic medical conditions or abnormal baseline laboratory values or a history of tic disorders, mental retardation (IQ <75), organic brain disorders, clinically unstable psychiatric conditions (ie, suicidal behaviors, psychosis, delinquency, criminality, or violence), or substance or alcohol abuse or dependence within the 6 months preceding the study or currently used psychotropics; also excluded pregnant or nursing women.
Spencer, 2001	103/41/30 Same subjects exposed to both treatments	Excluded clinically significant chronic medical conditions, abnormal baseline laboratory values, IQ less than 80, delirium, dementia, or amnestic disorders, any other clinically unstable psychiatric conditions (ie, bipolar disorder, psychosis), drug or alcohol abuse or dependence within the 6 months preceding the study, previous adequate trial of Adderall, or current use of psychotropics; also excluded pregnant or nursing females.
Spencer, 2005	289/NR/146	Subjects had clinically significant chronic medical conditions; abnormal baseline laboratory value; IQ<80; delirium, dementia, or amnestic disorders; other clinically unstable psychiatric conditions (i.e. bipolar disorder, psychosis, suicidality); drug or alcohol abuse or dependence within the 6 months perceding the study; previous adequate trial of stimulant (>0.5mg/kg/day of MPH or equivalent); or current use of other psychotropics. Pregnant or nursing women were also excluded.
Spencer, 1998	NR/NR/22	Exclusion criteria include clinically significant chronic medical conditions, abnormal baseline laboratory values, mental retardation (IQ<75), organic brain disorders, clinically unstable active psychiatric conditions, drug or alcohol abuse within the last 6 months, current use of psychotropics, and for women, pregnancy or nursing.

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

External Validity

Author, Year	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Schubiner, 2002	NR/NR	Unclear	Yes	National Institute on Drug Abuse Grant R01 DA 10271-03 and a Joe Young Srs. Research grant from the State of Michigan	Yes
Spencer, 1995	Run-in NR; 1-week washout between phases	No	Yes	Not reported	Yes
Spencer, 2001	Run-in NR; 1-week blinded placebo washout between phases	No	Yes	Shire Richwood Pharmaceuticals; NIMH grant	Yes
Spencer, 2005	NR/NR	Yes	Yes	NIMH and Novartis	Yes
Spencer, 1998	Run-in NR; 1-week washout between phases	NR	Yes	"Funded in part by Lilly Research Labs" and an NIMH grant	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity						
Author, Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Tenenbaum, 2002	Method NR	Method NR	Not reported	Yes	Yes but method not described	NR	Yes
Turner, 2004	Method NR	Method NR	Yes	Yes	Yes but method not described	Not reported	Yes but method not described
Weisler, 2006	Method NR	Yes	No; placebo group had significantly lower previous use of stimulants Also - Figure 2 (baseline characteristics) for the 'ITT' population only	Yes	NR	NR	Yes

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	*Internal Validity* Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis; If No: % analyzed	Post-randomization exclusions	Quality rating
Tenenbaum, 2002	Yes NR Yes NR	No/ no	No: 72.7%	No	Fair
Turner, 2004	Yes NR NR NR	No/ no	Yes	No	Fair
Weisler, 2006	NR NR NR NR	No/ no	No 183/255 (72%) analyzed	No	Poor

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

Author, Year	*External Validity* Number screened/ eligible/ enrolled	Exclusion criteria
Tenenbaum, 2002	128/85/33 Same subjects exposed to all treatments.	Potential participants were excluded if they had any clinically significant medical conditions such as heart condition, untreated thyroid condition, or tic disorder. Participants with active substance or alcohol abuse/dependence in the 6 months prior were also excluded. Other exclusions: pregnant or nursing females; neurological trauma or disorder (eg. concussion, epilepsy); chronic diseases; poor physical health; poor vision unless corrected. Individuals taking psychoactive medications (including methylphenidate) were excluded unless they discontinued such medications under the supervision of their prescribing physician for the duration of the study. Also excluded clients at the Attention Deficit Center, where all assessment and treatment sessions were conducted, due to potential conflict of interest. Excluded psychiatric disorders for which treatment with methylphenidate was contraindicated (e.g. panic disorder, major depression, moderate or more severe) or they were clinically unstable (e.g. suicidal behavior, psychosis, criminality/violence, bipolar disorder.
Turner, 2004	NR/NR/20 Enrolled in 1st treatment phase: 10 in modafinil, 10 in placebo	NART verbal IQ score <90, any significant visual or motor impairment, or the use of any medication contraindicated with modafinil. Patients were required to have no history of pervasive developmental disorders, neurologic disorders (including tic disorders), schizophrenia or psychotic disorders, bipolar disorder, or current major depressive disorder. Patients reported no substance abuse in the past 2 months. In addition, patients with a history of hypertension, cardiac disorder, or epilepsy. Patients were advised not to consume alcohol or caffeine for 12 hours before the study.
Weisler, 2006	339/259/255	Incapable of following study instructions; IQ <80; comorbid diagnosis if psychosis, bipolar illness, pervasive developmental disorder, severe OCD, severe depressive or anxiety disorder; positive drug screen, substance abuse history or living with someone with substance abuse disorder;glaucoma; hyperthyroidism; seizure; tic disorder or Tourette syndrome; pregnancy or lactation; use of any anticonvulsant drug, clonidine, guanfacince, systemic steroids, medications that affect BP, heart or CNS, pemoline or investigational drugs w/in 30 days of study

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

External Validity

Author, Year	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Tenenbaum, 2002	Run-in NR; 1-week washout between treatment phases	No, but excluded current use of MPH unless use was discontinued	Yes	Henkel Corporation	Yes
Turner, 2004	Run-in NR; 1-week washout between single-dose treatment phases	No	Yes	Wellcome Trust Program grant	Yes
Weisler, 2006	1 wk washout (medications not specified)	NO	Yes	Shire Pharmaceuticals	Yes

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)	Concomitant medication
Functional capacity					
Paternite 1999 (Fair)	Descriptive study Setting: University of Iowa outpatient child psychiatry clinic	Patients with diagnoses of hyperkinetic reactiont or a minimal braun dysfuncion syndrome were treated with MPH between 1967-1972	Mean=30.4 months range=1-76 months	MPH mean=32mg/day range=8-80mg/day	NR
Weiss 1975 (Fair)	Retrospective Cohort study Setting: the psychiatry depertment of the Montreal children's Hospital	Hyperactive children initially evaluated from 1962-1967 had been treated with methylphenidate, chlorpromazine, or none (group 1, 2 and 3).	Group 1: 51 months Group 2: 30 months	Group 1: MPH mean=30mg/day Group 2: chlorpromazine mean=75mg/day Group 3: none	NR
Lerer 1977 (Fair)	Before-After Setting: NR	Hyperactive children with IQ above 80 amd marked academic underachievement	60 days - 6 months	MPH mean=43mg/day range=40-60mg/day	NR

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Assessment Techniques	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Functional capacity				
Paternite 1999 (Fair)	General Interview structured interview by Loney Schedule of Affective Disorders and Schizophrenia (SADS-L) structured interview Interviewer: NR	Mean age=8.8 years Gender: 100% male Ethnicity: NR	219/121/97	NR/NR/97
Weiss 1975 (Fair)	Academic performance (reported cards rated by teachers)	Mean age= 7.96, 8.15 and 8.21 years (group 1, 2 and 3) Gender: NR Ethniciy: NR	NR/NR/150	NR/84/66
Lerer 1977 (Fair)	School grades (by teachers)	Mean age=15.5 years Gender: 92.6% male Ethnicity: 100% white	55/27/27	0/0/0

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Functional capacity	
Paternite 1999 (Fair)	Correlations with (a) "MPH dosage"; (b) "MPH response"; (c) "MPH duration" Psychiatric hospitalizations: none Suicide attempts: only (a) r= -0.23, p<0.05 Police contacts: none Emancipated living: only (b) r=0.31, p<0.05 Relationship commitment: only (b) r=0.25, p<0.05 High school graduation: only (b) r= -0.34, p<0.01 Post-secondary education: none Full employment: none Never fired from a job: none
Weiss 1975 (Fair)	Number of children in each group passing all grades or failing one or more grades: *Had never failed/ Had failed* Group 1: 13(54%)/11 Group 2: 9(41%)/12 Group 3: 6(30%)/14
Lerer 1977 (Fair)	15(55.6%) have shown impressive gains in behavior controla and academic achievement during this period of time, as documented by improvement in school grades. After 7-12 months of follow-up, only 2 have shown improvement. 3 have been temporarily or permanently suspended from school.

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)	Concomitant medication
Functional capacity					
Hecktman 1984 (Fair)	Retrospective Cohort study Setting: NR	6-12 years of age for sustained hyperactivity both at home and at school. Free of epilepsy, cerebral palsy, or psychosis	3 years between 6-12 years of age	MPH 20-50mg/day	NR

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Assessment Techniques	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Functional capacity				
Hecktman 1984 (Fair)	NR	Mean age=21.8 years Gender: NR Ethnicity: NR	NR/NR/104	0/84/20

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Functional capacity	
Hecktman 1984 (Fair)	Stimulant-treated hyperactives (STH), non-STH, Matched controls (MC): Demographic data: residential moves: STH>MC, p<0.05 live with girlfriends/wifes: STH>MC, p<0.02; STH>non-STH, p<0.01 future vacational plans or lower status plans: MC>STH, p<0.05 in debt: STH>MC, p<0.02 car accidents: non-STH>STH, p<0.004; STH vs MC, NS School: attending junior colleges and universities: MC>STH, p<0.05; STH>non-STH, p<0.03 fail grades in high school, STH>MC, p<0.1; STH vs non-STH, NS drop out school because of poor marks: STH>MC, p<0.08; STH vs non-STH, NS academic standing: MC>STH, p<0.05; STH vs non-STH, NS be expelled: STH>MC, p<0.07; STH vs non-STH, NS not in school because of lack of interests: non-STH>STH, p<0.05 Employer's Questionnaire get along with co-workers: STH>non-STH, no data reported being punctual, doing assigned work adequately, getting along with supervisors, completing tasks, and being rehired: all NS Work record: leave school ealier: STH>MC, p<0.028; STH vs non-STH, NS spend more time doing nothing: STH>MC, p<0.01; STH vs non-STH, NS have more job: STH>MC, p<0.01; STH vs non-STH, NS incomes: STH vs MC, NS; STH vs non-STH, NS greater debts: STH>MC, p<0.06; STH vs non-STH, NS longer period at last job: non-STH>STH, p<0.001 no problems with concentration: non-STH>STH, p<0.03 the percent of the work day: all NS full time jobs lasting less than 2 months, summer or part time jobs and reasons for leaving jobs: all NS

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)	Concomitant medication
Charles 1981 (Fair/poor)	Cross-sectional Setting: UCLA Department of Pediatrics	Children who had participated in a 16-week RCT of MPH vs placebo	4 years	Group 1: Stimulants < 6 months Group 2: Stimulants 6 mos to 2 years Group 3: Stimulants 2-3 years Group 4: Stimulants 3-4 years, but had discontinued ≥ 1 month prior to follow-up Group 5: Still on stimulants (MPH or pemoline)	NR
Persistence					
Bussing 2005	Prospective Cohort study Setting: NR	Children were eligible for the study if they lived in a household with a telephone, were not receiving special education services for mental retardation or autism, and were from Caucasian or African American backgrounds	12 months	NR	NR

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Assessment Techniques	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Charles 1981 (Fair/poor)	Teachers' responses to mail-based questionnaire	Mean age=12 years, 3 months 79% male 88.7% white 9.7% black 1.6% hispanic	98/70/62	n/a n/a Analyzed: Group1=13; Group2=10; Group3=14; Group4=13; Group5=12
Persistence				
Bussing 2005	Norbeck Social Support Questionnaire Caregiver Strain Questionnaire	Mean age = 8.1 (1.7) years 103(47%) male 68(31%) African-American	NR/12009/1615	NA/NA/220

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Charles 1981 (Fair/poor)	Group 1 vs 2 vs 3 vs 4 vs 5 Teacher reports of below grade level work (% children): Reading: 77 vs 75 vs 64 vs 73 vs 83 Spelling: 69 vs 75 vs 64 vs 55 vs 75 Mathematics: 69 vs 100 vs 56 vs 73 vs 58 Ability to sustain attention: 38 vs 75 vs 71 vs 73 vs 75 Unclear oral language: 15 vs 12 vs 14 vs 45 vs 50 Other Percentage of repeated grades (%): 46 vs 50 vs 36 vs 31 vs 8 Special education class placement: 31 vs 60 vs 36 vs 31 vs 58 Currently tutored: 15 vs 30 vs 14 vs 23 vs 41
Persistence	
Bussing 2005	**% of patients having ADHD medication at the time of phone interviews** (T2= the second phone interview, T3= the third phoneinterview) (AA=African-American, C= Caucasian) AA girls vs AA boys vs C girls vs C boys, p value T2: 10% vs 34% vs 28% vs 42%, p=0.006, B>G, AA<C T3: 15% vs 31% vs 19% vs 31%, p=0.147, B>G T2 or T3: 15% vs 41% vs 31% vs 47%, p=0.006, B>G **Predictors of Medication treatment: OR, p value, (95%CI)** Sociodemographic Gender(male): 2.75, p<0.05, (1.38-5.47) Race/Ethnicity(African American): 0.91(0.36-2.34) Age: 1.56(0.68-3.55) Need School Refferals: 1.03(0.98-1.09) Impairment Score: 1.02(0.97-1.07) Inattentive symptoms: 1.23, p<0.05, (1.05-1.43) Hyperactive/Impulsive Symptoms: 1.01(0.88-1.17) ODD or CD comorbility: 1.11(0.49-2.52) Parental Characteristics Average Instrumental Network Support: 0.69, p<0.001,(0.57-0.83) Global Caregiver Strain: 0.99(0.81-1.20)

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)	Concomitant medication
Lage 2004	Retrospective Cohort study Setting: NR Data resource: the Integrated Health Care information Services (IHCIS) National Manged Care Benchmark Database	1) Age 6-12 years at date of first prescription for XR MPH or TID IR MPH (index date); 2) patient-level data files containing information for at least 6 months before and 12 months after the index date; 3) no ADHD medications (i.e. amphetamine, dextroamphetamine, methylphenidate, imipramine, desipramine, clonideine, and bupropion) in the 6 months before the index date; and 4) no XR MPH use by the IR MPH group in the 12-month follow-up period.	NR	XR MPH TID IR MPH	NR
Marcus 2005	Retrospective Cohort study Setting: California Medicaid	Patients aged 6 to 17 years who were prescibed MPH and were eligible for California Medicaid benefits for at least 6 months preceding and 12 months following an index MPH prescription. Patients should not have a prescription claim for an ADHD medication during the 6 months preceding the index MPH prescription and did not have any inpatient claims during the follow-up period.	12 months	ER-MPH IR-MPH	NR

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Assessment Techniques	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Lage 2004	NR	Mean age=9.73 years 75% male Ethnicity: NR	NR/NR/NR	NR/NR/1775
Marcus 2005	sequentially counting the unduplicated continuous prescriptions using the date of the prescription and the number of days of medications supplied	Mean age: NR 70% 6-12 years 29% 13-17 years 78% male 45.3% White; 22.9% Black; 26.0% Hispanic; 5.7% Other	NR/NR/NR	NR/NR/11427

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Lage 2004	Treatment pattern- XR MPH vsTID IR MPH, p value Days supplied: 186 vs 127, p<0.0001 Discoutinue, stopped receiving all ADJD medications prior to t+1 year-28days: 47% vs 72%, p<0.0001 Switch, stopped prescription for one ADHD medication and started rescription another: 37% vs 59%, p<0.0001 Persist, no discontinuations or gap (>14days): 12% vs 1%, p<0.0001 Covariates of Accident/Injury- Coefficient, Odds ratio(95% CI) XR MPH: -0.5486, 0.578(0.353-0.945) Age(years): 0.1156, 1.123(0.994-1.267) Female: -0.9015, 0.406(0.225-0.734) Preferred provider: -0.5671, 0.567(0.365-0.882) Prior accidents present: 1.0576, 2.879(0.928-8.937) Prior total cost: -0.00024, 1.000(1.000-1.000) Number of chronic medications: -0.1480, 0.862(0.758-0.982) Number of diagnosis: 0.2286, 1.257(1.195-1.321) Intercept: -4.2703
Marcus 2005	Mean treatment duration- ER-MPH vs IR MPH, STR(95% CI) total: 140.3 vs 103.4, 1.37(1.32-1.42) Age 6-12y: 149.5 vs 107.5, 1.38(1.32-1.45) 13-17y: 125.1 vs 91.3, 1.35(1.27-1.43) Gender Male: 140.9 vs 101.8, 1.40(1.34-1.46) Female: 138.4 vs 109.1, 1.27(1.18-1.38) Race White: 154.9 vs 116.8, 1.43(1.35-1.52) Black: 125.7 vs 90.8, 1.37(1.27-1.48) Hispanic: 126.2 vs 94.9, 1.28(1.19-1.38) Other: 130.4 vs 93.9, 1.29(1.10-1.53)

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)	Concomitant medication
Sanchez 2005	Retrospective Cohort Texas Medicaid prescription claims database	Texas Medicaid recipients aged 5-18 years with continuous paid prescription claims from June 1, 2001-May 31, 2002; new to stimulant therapy (no stimulants dispensed for at least 60 days prior to index prescription); and at least one dispensed prescription for MPH IR, MPH SR, MPH ER, MPH OROS, MAS IR, DEX IR, DEX ER	6 months	MPH IR, MPH SR, MPH ER, MPH OROS, MAS IR, DEX IR, DEX ER	NR
Kemner 2006	Retrospective Cohort Data source: Integrated Health Care Information Services National Managed Care Benchmark Database Data collection period: 2/1/00-12/31/02	ICD-9 code 314.00 or 314.01 for diagnosis of ADHD; newly initiated on ER or IR MPH (no ER or IR MPH use in preceding 6 months); ≥ 6 years of age; continuous insurance coverage with same plan during the study periods	12 months	MPH IR 30 mg vs MPH ER 36 mg	NR

Race

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Assessment Techniques	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Sanchez 2005	**Persistence:** number of days from date of the first prescription to the end of the treatment period of the last prescription for each stimulant divided by the defined treatment window of 6 months; breaks in treatment of longer than 15 days constituted end of treatment period **Medication Possession Ratio (MPR):** actual number of days of therapy divided by the optimum number of days of therapy	Mean age=9.93 years 75.7% male Ethnicity NR	NR/NR/9,549	N/A
Kemner 2006	**Medication usage patterns:** 1) Gaps in therapy of ≥ 15 days 2) Switches to alternative ADHD medications 3) Number of days on therapy 4) Adherence: percentage of patients receiving ER and IR MPH for 75%, 80%, and 90% of post-initiation period **Treatment patterns:** emergency room visit	Mean age=15 years 77% male Race NR	NR/NR/5939	NR/NR/5939

Race

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Sanchez 2005	Comparisons among stimulant groups (MAS IR vs MPH IR vs MPH OROS) Persistence: 0.42 vs 0.37 vs 0.50 (F=159, df=2, p<0.0001) MPR: 0.73 vs 0.69 vs 0.76 (F=32, df=2, p<0.001) 150-180 day treatment duration (% pts): 19% vs 14% vs 30% (χ^2=327, df=10, p<0.00) Comparisons among age groups for all drugs combined (5-9 yrs vs 10-14 yrs vs 15-18 yrs) Persistence: 0.45 vs 0.41 vs 0.41 (F=21.6, df=2, p<0.001) MPR: 0.73 vs 0.73 vs 0.67 (F=11.8, df=2, p<0.001)
Kemner 2006	ER vs IR MPH: Mean duration on therapy (# days): 199 vs 107, p<0.0001 % patients with 15-day gap: 85% vs 97%; p<0.0001 % patients with 30-day gap: 77% vs 9%; p<0.0001 Switch to other formulation: 1% vs 33%; p<0.0001 % patients 75%/80%/90% adherent: 30%/29%/24% vs 7%/7%/5%; p<0.0001 for all % patients who visited the emergency room: 20.9% vs 22.4%, NS OR (95% CI) of an emergency room visit: ER MPH: 0.79 (0.60, 0.95), p=0.01 Comorbid diagnoses: Anxiety: 1.09 (0.53, 2.24) Depression: 0.93 (0.48, 1.79) ODD: 1.31 (0.095, 1.81) Drug or alcohol abuse: 2.59 (1.61, 4.17), p<0.0001 Accident or injury: 37.97 (28.16, 51.20), p<0.0001

Race

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Design	Eligibility criteria	Duration	Interventions (mean dose)	Concomitant medication
Lee 2006	Prospective, open-label, before-after study	Full diagnosis of ADHD based on DSM-IV criteria; moderate to severe level of impairment; drug naïve or not medication at least 6 months before study initiation; no abnormalities in baseline physical examination and routing laboratory tests; IQ of at least 70 (Korean Wechsler Intelligence Scale for Children); no suspected or confirmed substance abuse; absence of other clinically significant medical or psychiatric illness	4 weeks	MPH OROS	Use of other alpha-2 adrenergic receptor agonists, TCA's, theophylline, coumarin or anticonvulsants prohibited

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Assessment Techniques	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Lee 2006	**Primary:** IOWA Conners' Rating Scale, Parent and Teacher versions, standardized into Korean version, CGI-S, peer interaction items **Secondary:** CPT, Matching Familiar Figure Test, Verbal Fluency Test, Trail Making Test	Mean age=8.5 years 90% male 100% Korean	NR/NR/119	9 (7.6%) withdrawn/0 LTFU/110 analyzed

Evidence Table 13. Observational studies - functional outcomes

Author Year Country	Outcomes
Lee 2006	Mean scores at baseline/endpoint (all p<0.001) Parent IOWA Conners I/O: 6.9/3.9 IOWA Conners O/D: 5.6/2.7 Teacher IOWA Conners I/O: 7.0/3.9 IOWA Conners O/D: 4.9/2.7 Peer Interaction Items: 6.1/3.2 Clinician CGI-S: 4.3/3.1

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Non-biased selection?	For studies with ≥ 2 groups: Similar at baseline?	Eligibility criteria specified?	Attrition specified?	Loss to follow-up specified? If yes, low overall loss to follow-up?
Bussing 2005	Yes	n/a	Yes	Yes	No
Charles 1981	No: excluded 36 (36.7%)	n/a	No	n/a	n/a
Gau 2006	Yes; 88% or target recruited	NA (cross sectional study)	Yes	Yes; 18.1%	NR; attrition due to 'not currently treated with" ADHD drug
Hecktman 1984	Yes	No	Yes	Yes	Yes No
Kemner 2006/Lage 2004	Yes	No; ER group was significantly younger and had a significantly higher total number of diagnoses in the 6-month preinitiation period	Yes	Hospitalization data was analyzed for 100% of patients; unclear if all other data points were available for all patients	NR

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Bussing 2005	Yes	Yes	Yes	Yes	Yes
Charles 1981	No	No	No	No	Yes
Gau 2006	Yes	Yes	Yes; questionnaires administed to patients and families	Yes; regression model of predictors for drug adherence; poor and good adherence groups compared; controlled for age, sex, education	Yes, 1 month
Hecktman 1984	Yes	No	Unclear	No	Yes
Kemner 2006/Lage 2004	Yes	Yes	Yes	Yes; controlled for demographic characteristics, general health status, comorbid diagnoses associated with diagnosis of ADHD and use of ADHD medications	Yes

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Overall quality rating
Bussing 2005	Fair
Charles 1981	Fair-Poor
Gau 2006	Fair
Hecktman 1984	Fair
Kemner 2006/Lage 2004	Fair

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Non-biased selection?	For studies with ≥ 2 groups: Similar at baseline?	Eligibility criteria specified?	Attrition specified?	Loss to follow-up specified? If yes, low overall loss to follow-up?
Lage 2004	Yes	No; XR group older, more HMO use, more chronic medications and diagnoses, and higher prior total medical costs	Yes	n/a	n/a
Lee 2007	Unclear as to how many were eligible compared to how many were enrolled	N/A	Yes	Yes	Yes/Yes
Lerer 1977	No: excluded 11 (41%) nonresponders	n/a	Yes	Yes	No
Marcus 2005	Unclear	No; ER group patients received treatment for a mental disorder other than ADHD during the 6 months preceding the index prescription and more likely to have been prescribed antidepressants, antipsychotic medications, and mood stabilizers during the follow-up period	Yes	n/a	n/a

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?
Lage 2004	Yes	Yes	Yes	Yes	Yes
Lee 2007	Yes	Yes	Yes	N/A	Yes
Lerer 1977	Yes	No	Unclear	NR	Yes
Marcus 2005	Yes	Yes	Yes	Yes	Yes

Evidence Table 14. Quality assessment of observational studies - functional outcomes

Author	Overall quality rating
Lage 2004	Fair
Lee 2007	Fair
Lerer 1977	Fair
Marcus 2005	Fair

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Elementary School Children - Atomoxetine (tomoxetine)			
Kratochvil 2001 U.S. (Fair)	Before-after, prospective Setting: 1 of 24 clinical research sites involved in an ongoing multicenter study	DSM-IV criteria for ADHD	10 weeks

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Elementary School Children - Atomoxetine (tomoxetine)			
Kratochvil 2001 U.S. (Fair)	Tomoxetine mean dose nr	NR	Weight measured at weekly clinic visits

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Elementary School Children - Atomoxetine (tomoxetine)			
Kratochvil 2001 U.S. (Fair)	Mean age NR 100% male 90% White 10% Hispanic	NR/NR/100	2 (20%) withdrawn 0 lost to fu 10 analyzed

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Elementary School Children - Atomoxetine (tomoxetine)	
Kratochvil 2001 U.S. (Fair)	Weight change (mean change): -0.15 kg, p=NS

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Elementary School Children - Atomoxetine (tomoxetine)	
Kratochvil 2001 U.S. (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Elementary School Children - Methylphenidate			
Brehaut 2003 Canada (Fair)	British Columbia Linked Health Dataset (BCLHD)	January 1, 1990 and December 31, 1996	NR

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Elementary School Children - Methylphenidate			
Brehaut 2003 Canada (Fair)	Methylphenidate (mean dose NR)	Any individual who was <19 years of age on December 31, 1996. Children were included in the childhood behavior disorder (CBD) group if they were listed as having been prescribed MPH at least once between January 1, 1990 and December 31, 1996. All other children and youth were included in the no CBD group.	51.4% male <4 y=18.2% 4-8, 11 mo=27.2% 9-13 y, 11 mo=27.4% 14-18 y, 11 mo=27.1% Ethnicity NR

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Elementary School Children - Methylphenidate			
Brehaut 2003 Canada (Fair)	1,028,028 exposed Eligible NR Selected=1,026,873		

Evidence Table 15. Observational studies - long-term safety

Author
Year
Country **Safety outcomes**

Elementary School Children - Methylphenidate
Brehaut
2003
Canada
(Fair)

Injury	No CBD Frequencies (n=1,010,067)	CBD Frequencies (n=16,806)	Odds Ratios 99% CI	Logistic Regression Odds Ratios 99% CI
Nature of injury				
Fractures	20,025 (2.0%)	723 (4.3%)	2.22 2.01-2.46	1.42 1.27-1.58
Open wounds	4858 (0.5%)	224 (1.3%)	2.80 2.34-3.34	1.89 1.56-2.29
Poisoning/toxic effect	3882 (0.4%)	184 (1.1%)	2.87 2.36-3.49	2.67 2.16-3.30
Intracranial	2675 (0.3%)	107 (0.6%)	2.41 1.87-3.11	1.66 1.27-2.19
Concussion	2667 (0.3%)	127 (0.8%)	2.88 2.27-3.64	1.82 1.42-2.35
Burns	1301 (0.1%)	45 (0.3%)	2.08 1.41-3.08	1.99 1.31-3.02
Total	32,242 (3.2%)	1,257 (7.5%)	2.45 2.27-2.65	1.67 1.54-1.81
Cause of injury				
Falls	16426 (1.6%)	573 (3.4%)	2.14 1.91-2.39	1.46 1.29-1.64
Postoperative complications	6166 (0.6%)	168 (1.0%)	1.64 1.34-2.01	1.37 1.10-1.71
Struck by object	4146 (0.4%)	157 (0.9%)	2.29 1.85-2.82	1.35 1.07-1.69
Motor vehicle accident	3333 (0.3%)	136 (0.8%)	2.46 1.97-3.09	1.56 1.23-1.99
Adverse effects	2370 (0.2%)	87 (0.5%)	2.21 1.67-2.93	2.12 1.58-2.85
Nonmotor vehicle pedal	2360 (0.2%)	118 (0.7%)	3.02 2.37-3.85	1.71 1.33-2.22
Suffocation	813 (0.1%)	23 (0.1%)	1.70 0.99-2.93	2.02 1.13-3.60
Drowning	185 (<0.1%)	6 (<0.1%)	1.95 0.67-5.68	1.75 0.59-5.17
Total	33855 (3.4%)	1180 (7.0%)	2.18 2.01-2.36	1.52 1.40-1.66

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Elementary School Children - Methylphenidate Brehaut 2003 Canada (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Gadow 1999 U.S. (Fair)	Long-term follow-up to participation in an 8-233k controlled trial of methylphenidate and placebo Setting: NR Noncomparative	DSM-III-R diagnostic criteria for ADHD and either chronic motor tic disorder and, in general, were above cutoff on 2 of 3 parent-completed and 2 of 3 teacher-completed	2 years

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Gadow 1999 U.S. (Fair)	Methylphenidate Short-term dose trial mean dose: 8.3 mg Long-term follow-up mean dosages: 6 months=13.3 mg 12 months=16.2 mg 18 months=29.2 mg 24 months=34.5 mg	NR	Height Weight Tics

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Gadow 1999 U.S. (Fair)	Short-term dose trial (n=34) Mean age=8.8 91.2% male Race NR	NR/NR/34	Number of subjects at each follow-up visit/number receiving stimulants: 6 months=28/27 12 months=33/30 18 months=29/26 24 months=29/26 (1 switched to dextroamphetamine)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Gadow 1999 U.S. (Fair)	Weight in kg (mean expected/actual/difference/p-value): 41.95/41.23/0.72/p=0.59 Height in cm (mean expected/actual/difference/p-value): 147.48/146.81/0.67/p=0.57 Tic measurements (diagnostic/placebo/6 month/12 month/18 month/24 month) YGTSS Total Motor Tics: 13.9/11.4/12.1/12.2/13.0/12.6 Total Phonic Tics: 11.2/7.9/7.6/8.1/8.3/8.0 Overall Improvement Rating: 19.5/7.6/9.7/9.4/10.2/8.5 Global Severity Scale: 42.9/26.5/27.1/30.0/31.3/29.9 STESS: 2.9/1.6/1.8/2.0/1.9/1.9 TS-CGI: 2.6/3.1/3.1/2.3/2.4/2.3 TS unified Rating Scale: Shapiro Symptom Checklist No of Motor Tics: 13.2/11.7/12.0/12.8/14.0/13.4 No. of Vocal Tics: 5.0/3.1/2.5/2.9/2.8/2.5 2-Minute Tic Count Motor Tic Count: 10.0/9.5/13.8/14.4/18.1/17.2 Vocal Tic Count: 1.1/0.6/0.4/1.1/1.3/1.5 GTRS Motor Tic Index: 4.8/4.9/5.0/5.0/4.8/4.8 Vocal Tic Index: 1.9/1.0/1.1/1.1/1.4/1.4 Tic Severity Index: 3.2/1.4/1.8/2.2/2.5/2.6 LeWitt Disability Scale: 61.9/68.6/72.9/72.4/70.7/73.1 CGI-OC: 2.7/1.6/1.8/1.7/1.9/1.8 Parent Ratings GTRS Motor Tic Index: 3.7/2.2/2.4/3.2/2.5/2.4 Vocal Tic Index: 1.8/0.9/0.9/1.2/0.8/0.6 Tic Severity Index: 3.3/1.6/1.8/2.4/1.9/2.1 Classroom observations: Motor Tic Frequency: 18.6/18.6/23.8/21.0/21.0/19.5/18.9

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Gadow 1999 U.S. (Fair)	Only 2 comparisons indicated that tics were worse on medication than placebo (data nr)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Quinn 1975 U.S. (Fair)	Unblinded follow-up of samples that continued their original randomly assigned medication (6-week, randomized, DB study: Rapoport, 1974) Setting: Hyperactivity Clinic Noncomparative	NR	1 year

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Quinn 1975 U.S. (Fair)	Methlyphenidate mean daily dose of 20.56 mg Imipramine mean daily dose of 65.4 mg	NR	Height Weight Seizures

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Quinn 1975 U.S. (Fair)	Mean age nr 100% male Race NR	NR/NR/75	28 (37.3%) withdrawn overall/lost to fu=0

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Quinn 1975 U.S. (Fair)	Safety compared only for children initially assigned to the active drug group and continued on the same medication for one year (methylphenidate n=23; imipramine n=13) Anorexia: 9 (47%) vs 5 (39%) Seizures: none reported Condition 1=Imipramine Condition 2=methylphenidate all doses (n=23) Condition 3=methylphenidate > 20 mg a day (n=5) Condition 4=methylphenidate 20 mg a day or less (n=18) Condition 5=no treatment (n=12) Weight change (percentile scores): -7.54 vs -8.81 vs -15.40 vs -6.88 vs +1.61 t-scores, p-values for comparisons of condition 5 with 1; 2; 3; 4: 2.45, p<0.01; 3.42, p<0.005; 4.18, p<0.005; 3.44, p<0.005 t-scores, p-values for comparisons of condition 1 with 2; 3; 4: .37, p=NS; 1.27, p=NS; 0.19, p=NS Height changes (percentile scores): -2.20 vs +3.19 vs -3.0 vs +5.12 vs -1.46 t-scores for comparisons of condition 5 with 1; 2; 3; 4 (p-values all NS): 0.23; 1.05; 0.22; 1.59 t-scores, p-values for comparisons of condition 1 with 2, 3, and 4: 1.25, p=NS; 0.12, p=NS; 1.90, p<0.05

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Quinn 1975 U.S. (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Mattes 1983 U.S. (Fair)	Before-after (open trial of methylphenidate) Setting: NR Noncomparative	Children had to be considered hyperactive both in school and at either home or the clinic; furthermore, a high level of disruptive behavior was required	Up to 4 years Duration of treatment (weeks): Up to 1 year: 20.7 1-2 yr: 59.4 2-3 yr: 99.1 3-4 yr: 130.0

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Mattes 1983 U.S. (Fair)	Methylphenidate mean dosages (mg): Up to 1 year: 39.9 1-2 year: 41.3 2-3 year: 41.0 3-4 year: 41.4	Thioridazine hydrochloride received by 34 (39.5%) at some time during the study	Changes in weight and height percentiles

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Mattes 1983 U.S. (Fair)	Mean age NR Gender NR Race NR	NR/NR/86	44 (51.2%) withdrawn by end of year 4

Evidence Table 15. Observational studies - long-term safety

Author
Year
Country **Safety outcomes**

Mattes
1983
U.S.
(Fair)

Year	N	Pretreatment	End of year	t	p	Correlation with treatment duration (Pearson's r, p-value)	Correlation with mean daily dose (Pearson's r, p-value)	Correlation with total cumulative dose (Pearson's r, p-value)
Height								
1	51	51.1	49.7	1.56	NS	-.20, NS	0.04, NS	-0.17, NS
2	56	51.7	43.6	7.10	<0.001	0.18, NS	0.09, NS	0.16, NS
3	37	60.5	47.1	8.13	<0.001	0.04, NS	0.29, NS	0.24, NS
4	19	66.6	48.5	6.50	<0.001	0.33, NS	0.15, NS	0.28, NS
Weight								
1	69	59.2	49.5	6.81	<0.001	0.17, NS	0.17, NS	0.26, p<0.05
2	69	57.4	41.5	9.24	<0.001	0.31, p<0.01	0.12, NS	0.29, p<0.05
3	44	62.1	43.5	10.18	<0.001	0.05, NS	0.05, NS	0.09, NS
4	26	62.5	41.9	5.82	<0.001	0.39, p<0.05	-0.01, NS	0.018, NS

Multiple regression analysis of relationship of dosage and final height (n=42, includes 6 children who were off MPH at 3 years)

Step	Factors	Multiple correlation	Total explained variance (%)	Unique variance contribution of each factor (%)
1	Baseline height	0.94	87.8	87.8 (Pearson's r)
2	Baseline weight	0.94	88.2	0.4
3	Age at final height measurement	0.94	88.3	0.0
4	Baseline age	0.94	88.5	0.2
5	Total cumulative dosage of MPH	0.95	90.5	2.0 (p<0.01)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Mattes 1983 U.S. (Fair)	Once a year the methylphenidate regimen was replaced by a single-blind placebo trial. Only children whose behavior clearly deteriorated while they received placebo were returned to active treatment. Many of the children discontinued the medication regimen during the summer; methylphenidate therapy was reinstated in the fall only if behavioral complaints from school were received.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Wernicke 2003 U.S. (Fair)	Pooled analyses of (1) 3 short-term trials in children/adolescents (Spencer 2002, Michelson 2001); (2) 2 short-term trials in adults (Michelson 2003); and (3) long-term, open-label extensions or a blinded continuation following the three short-term treatment trials The short-term QTc-interval and cardiovascular adverse events data were not reported in the original publications	Children and adolescents with ADHD	At least 1 year

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Wernicke 2003 U.S. (Fair)	Atomoxetine maximum dosage of 2 mg/kg/day administered in two divided doses (mean dose nr)	NR	QT interval prolongation using Bazett (exponent of 0.5) and Fridericia (exponent of 0.33) corrections. Categorical changes (increases of at least 30, 60, or to at least 500 msec) are those proposed by the European CPMP

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Wernicke 2003 U.S. (Fair)	Children/adolescents (n=550) Mean age=10.5 75.1% male 78.5% white Adults Mean age=41.1 64.9% male 90.8% white Long-term population data nr	NR/NR/NR	NR/NR

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Wernicke 2003 U.S. (Fair)	Baseline change in corrected (Friderida formulat) QT intervals: short-term treatment atomoxetine vs placebo, p-value Children (n=325 vs n=202): QTcD, mean change at endpoint: -3.1 vs -4.4, NS QTcD, increase > 30msec: 2.2% vs 4.5%, NS QTcD, increase > 60 msec or > 500 msec: NR QTcB, mean change at endpoint: 1.5 vs -4.5, p=0.004 QTcB, increase > 30 msec: 6.2% vs 7.4%, NS QTcB, increase > 60 msec: 0.3% vs 1.0%, NS QTcB, increase > 500 msec: NR QTcF, mean change at endpoint: -5.3 vs -4.4, NS QTcF, increase > 30 msec: 1.8% vs 2.5%, NS QTcF, increase > 60 msec or > 500 msec: NR Adults (n=257 vs n=257) QTcD, mean change at endpoint: 0.6 vs 0.8, NS QTcD, increase > 30msec: 2.3% vs 3.5%, NS QTcD, increase > 60 msec or > 500 msec: NR QTcB, mean change at endpoint: 5.7 vs 0.6, p<0.001 QTcB, increase > 30 msec: 6.2% vs 4.7%, NS QTcB, increase > 60 msec: 0.0% vs 0.0%, NS QTcB, increase > 500 msec: NR QTcF, mean change at endpoint: -2.7 vs 0.9, p=0.008 QTcF, increase > 30 msec: 1.2% vs 2.7%, NS QTcF, increase > 60 msec or > 500 msec: NR Long-term treatment group: "There is no evidence of an increase in QTc with increasing dosage of atomoxetine as indicate Number of patients with treatement-emergent cardiovasculatr adverse events, atomoxetine vs placebo, p-value: Children (n=340 vs n=207): Palpitation:0.3% vs 0%, NS Tachycardia:0.9% vs 0%, NS Cardiac murmur: 0.6% vs 0%, NS Extrasystoles: 0% vs 0%, NA

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Wernicke 2003 U.S. (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Gross 1976 U.S. (Fair)	Retrospective analysis of height and weight data among 100 children treated for at least 2 years for ADHD, and with mean follow-up of 6 years. Setting: NR Comparative	Eligible subjects were children and adolescents diagnosed with hyperkinetic syndrome or minimal brain dysfunction within the investigator's clinical practice. To be included in the study required that a measurement of weight and height be available within 1 year prior to the onset of pharmacotherapy; 91% of measurements were within 6 months of treatment.	Subjects received at least 2 (mean=5) years of treatment. Mean follow-up time: 5.8 years for MPH, 6.8 years for dextramphetamine.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Gross 1976 U.S. (Fair)	Methylphenidate mean dose 34 mg/day, n=60 Dextroamphetamine mean dose 16.5 mg/day, n=24 (Imipramine/desipramine, n=16)	NR	Changes in weight and height percentiles, compared with Iowa city norms

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Gross 1976 U.S. (Fair)	Mean age at onset of treatment: 9 Gender 82% Ethnicity NR At final measurement, 45% were aged 1 6+ 17% were aged 18+	NR/NR/100	NR/NR/100

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Gross 1976 U.S. (Fair)	Average in percentile of weight, MPH vs detroamphetamine: Time after onset: 1 year: -5.2 (p<0.05) v 2 year: -4.3 (NS) vs -6 3 year: -3.0 (NS) vs

Methylphenidate group: changes in percentiles of weight and height

Time after onset (yrs)	N on medication	Mean daily dose	Average change in percentile (p-value)	
			Weight	Height
1	60	24.4	-5.2 (p<0.05)	-0.1 (ns)
2	60	31.7	-4.3 (ns)	+0.4 (ns)
3	54	38.5	-3.0 (ns)	-1.9 (ns)
4	44	43.3	+7.5 (ns)	+7.0 (ns)
5	35	47.2	+7.2 (ns)	+7.1 (ns)
6	24	51.2	+10.4 (ns)	+8.9 (ns)
7	15	40.0	+24.4 (p<0.05)	+14.9 (p<0.05)
8	6	40.0	+19.1 (p<0.05)	+12.2 (p<0.05)
At final f/u (mean 5.8y)	30	43.8	+11.4 (p<0.001)	+12.8 (p<0.001)
Dextroamphetamine group: changes in percentiles of weight and height				
1	24	12.2	-5.9 (p<0.05)	-1.8 (ns)
2	24	14.5	-6.0 (ns)	+0.8 (ns)
3	24	17.7	-3.4 (ns)	+1.9 (ns)
4	22	18.9	+2.2 (ns)	+5.2 (ns)
5	15	20.1	+3.2 (ns)	+6.2 (ns)
6	12	16.7	+9.3 (ns)	+9.8 (ns)
7	6	18.0	+18.1 (ns)	+13.4 (ns)
8	4	20.0	+10.5 (ns)	+13.2 (ns)
9	2	25.0	+41.0 (ns)	+17.3 (ns)
At final f/u (mean 6.8y)	12	19.6	+16.0 (p<0.02)	+10.9 (p<0.01)

Patients who had discontinued medication at final follow-up had larger increments in percentiles for both height and weight compared with patients still taking medication, but differences were not significant.
Analysis by age at treatment onset found that older children made greater gains in weight and height percentiles than younger children, but the difference was not statistically significant.
Correlations between mean dose during treatment vs. change in percentile from onset to final follow-up, and between age at onset of treatment vs. change in percentile from onset to final follow-up, were low in magnitude (0.03 to –0.22 for *r*) and not significant.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Gross 1976 U.S. (Fair)	Loss of weight compared with expected norms occurs during the first 3 years with MPH and dextroamphetamine, but there is a statistically significant increase in weight and height percentiles at final measurement in both treatment groups. Compliance was assessed by checking prescription records.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Safer 1972 U.S. (Fair)	Retrospective analysis of height and weight data among 2 groups: 1) hyperactive children who had been on stimulant medication for 9 months and had been either kept on or taken off treatment during the 3-month summer period; 2) hyperactive children, some who received continuous medication for 2+ years, and some who received no medication. Setting: NR Comparative	Group 1: 20 hyperactive children in an elementary school who were known by the school nurse to be regularly taking either methylphenidate or dextroamphetamine for hyperactivity. Group 2: 9 hyperactive children who had been on medication continuously for 2 or more years, and 7 children who although referred for stimulants were not given any owing to parental objection.	Group 1: 1 year Group 2: 2+ years

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Safer 1972 U.S. (Fair)	Group 1: Methylphenidate 28.7 mg/day Dextroamphetamine 11.8 mg/day Group 2: Methylphenidate continuous treatment for 2+ years (dose not reported; 7 of 9 subjects were also in group 1 above) Control group: no medication	NR	Group 1: Height and weight were recorded in September, 1970 at the beginning of the school year, June 1971 before summer vacation, and again in September 1971. Group 2: The nurse obtained past height and weight measurements from school admission information at the age of five or six.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Safer 1972 U.S. (Fair)	Group 1: Mean age 9.8 Gender NR 100% white Group 2: Mean age NR Gender NR Ethnicity NR	NR/NR/29: 20 in Group 1, 16 in Group 2, with 7 occurring in both groups	NR/NR/29

Evidence Table 15. Observational studies - long-term safety

Author
Year
Country **Safety outcomes**

Safer
1972
U.S.
(Fair)

Group 1	N	Dose of MPH mg/day	Dose of DAMP mg/day	Weight gain in school year (Sept-June), kg/mo		Weight gain in summer (June-July-Aug), kg/mo		
				All patients	All on MPH vs all on DAMP	All patients	Patients on MPH	Patients on DAMP
Continued meds. in summer	7	37.5	11.7	0.15	0.23 vs 0.12 (p<0.05)	0.22 (60% of expected gain)	0.29	0.14
Discontinued meds. in summer	13	24.0	11.8	0.17		0.45 (130% of expected gain)	0.41	0.47
P-value, Continued vs Discontinued		p<0.05	ns	ns		p<0.05	ns	p<0.01

Group 2	N	Average percentile changes in growth over 2 or more years		
		Weight	Height	
Medication 2+ years	9	-17.5	-16.3	Mean yearly weight gain of children on stimulants for 2 years was 1.8kg, compared with expected gain of 3.1 kg. Mean percentile for weight decreased from 62nd to 40th.
No medication	7	+1.3	+4.0	
P-value, Medicated vs. Not		p<0.05	p<0.05	

DAMP's effects on weight gain did not differ between doses of 10 and 15 mg/day.
MPH 20 mg/day showed significantly greater weight gains than 30 and 40 mg/day.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Safer 1972 U.S. (Fair)	The school nurse determined the use of medication during summer based on the children's self-report. At the start of the following school year, the nurse would ascertain if their parents had kept them on medication during the summer.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Satterfield 1979 U.S. (Good)	Prospective study of weight and height in boys treated for two years with methylphenidate. Setting: clinic, single-site Noncomparative	Subjects were all children who were referred to Gateways Hospital Hyperkinetic Children's Clinic, Los Angeles, from September 1973 thru December 1974, and met the following criteria: boys aged 6-12, attending school, having normal vision and hearing, of normal intelligence on the Wechsler Intelligence Scale for Children (80+); hyperactive by behavioral criteria that required evidence of chronic symptoms of hyperexcitability, impulsivity, and poor attention span, as reported by parents and teachers; nonpsychotic, non-brain-damaged. 20% of subjects had received stimulant drugs prior to entering the study.	2 years

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Satterfield 1979 U.S. (Good)	Methylphenidate, taken bid (morning and noon) on 5 weekdays; some patients required a third dose midafternoon, and others required medication 7 days/week. Some children took the medication only during the school year; others continued medication during the summer but at a lower dosage. Mean dose, year 1: 24.2 mg/day, 0.47 mg/kg/day Mean dose, year 2: 0.59 mg/kg/day	NR	Initial height and weight measures were converted to percentile rank based on the Iowa growth tables for normal children. Using these tables, this percentile rank predicted height and weight at years 1 and 2 for each subject. Expected gains for years 1 and 2 were computed based on initial and predicted percentiles. Growth deficits were computed from predicted vs observed growth. Monthly weight and height measurements were obtained by research staff on a pediatric scale, with child's shoes removed and pockets emptied. All measurements were used to determine growth rates and total year's growth.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Satterfield 1979 U.S. (Good)	Age range 6-12, mean age NR 100% male Ethnicity NR	NR/NR/72	NR/NR/72 72 analyzed in year 1 48 analyzed in year 2

Evidence Table 15. Observational studies - long-term safety

Author
Year
Country

Safety outcomes

Satterfield
1979
U.S.
(Good)

Patient group	N	Mean dosage mg/kg/day	Growth difference in % of expected growth (p-value); mean difference	
			Weight	Height
Year 1				
Total	72	0.47	-29% (p<0.01) 0.85 kg less	-19% (p<0.001) 1.03 cm less
Received summer med.	31	0.627	-35% (p<0.05)	-17% (p<0.05)
No summer medication	41	0.37	-24.5% (p<0.05)	-19.5% (p<0.05)
Year 2				
Total	48	0.59	-10% (ns) 0.31 kg less	+8% (ns) 0.42 cm more
Received summer med.	24	0.81	-20% (p<0.05) 0.67 kg less	+7.5% (ns) 0.36 cm more
No summer medication	24	0.37	+2.5% (ns) 0.25 kg more	+10% (ns) 0.49cm more
Accumulated growth: Year 1 plus Year 2				
Total	48	0.56	-13% (ns)	+2% (ns)
Height and weight deficits in year 1 and in year 2 were not significantly correlated with average daily dosage, age, or before-treatment height or weight. Height and weight deficits in the first year were not significantly correlated with similar deficits in the second year of treatment.				

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Satterfield 1979 U.S. (Good)	Adherence in 93% of patients was confirmed by monthly urinalysis. Significant deficits in growth were observed in the 1st year. Greater-than-expected gains in height and weight occurred in the 2nd year of treatment, though these increases were not statistically significant.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
McNutt 1976a (preliminary report) McNutt 1976b U.S. (Fair)	Long-term follow-up anterospective study of subjects in short-term studies on the effects of different doses of methylphenidate Setting: Physical Fitness Research Laboratory at Institute for Child Behavior and Development, University of Illinois at Urbana-Champaign	Hyperactive children on methylphenidate that had been subjects in short-term studies	≥ 8 months of medication during a 12-month period ≥ 16 months of medication during a 24-month period

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
McNutt 1976a (preliminary report) McNutt 1976b U.S. (Fair)	Methylphenidate mean daily doses: 12-month cohort: 24.1 mg 24-month cohort: 29.1 mg Dosing schedule NR	NR	Height: measured with a stadiometer and recorded in cm to the nearest mm; taken while the subject was standing with heels together with the body help in a maximally erect position and hands on the hips with a maximal inspiration of air Weight: after urine was voided, measured with the subject standing on a platform scale (Howe-Richardson) attired in standard lightweight gym shorts and barefooted; determined to the nearest grams Body composition: subcutaneous fat, body girth, and skeletal width were all made on the right side of the body; body fat and lean body mass were estimated from body weight and upper arm and back skinfold thicknesses according to regression equations established by Lohman; two thicknesses of skin and subcutaneous fat were included; reading from the calipers were recorded to the nearest mm and the mean of 3 readings at each site was rounded to the nearest 0.1 mm and used as the representative reading

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
McNutt 1976a (preliminary report) McNutt 1976b U.S. (Fair)	Medicated (n=28) vs nonmedicated (n=24) vs control (n=47) vs overall <u>12-month</u> Mean age: 10.5 vs 10.7 vs 9.71 vs 10.2 % male: 85.7% vs 87.5% vs 68% vs 77.8% Race nr <u>24-month</u> Mean age: 10.1 vs 9.7 vs 9.87 vs 9.9 % male: 84.6% vs 90% vs 85.7% vs 86.5% Race nr	NR NR NR	NR NR 12 months: medicated n=28, nonmedicated n=24, control n=47 24 months: medication n=13, nonmedicated n=10, control n-14

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
McNutt 1976a (preliminary report) McNutt 1976b U.S. (Fair)	12 months Growth (age, height, and weight): medicated=controls (data nr); Analysis of covariance (with age as covariate): medicated=controls (data nr); medicated=nonmedicated Lean body mass, percent body fat, body girth: medicated=controls; Analysis of covariance (with age as covariate): medicated=controls (data nr); medicated=nonmedicated Skeletal width: hyperactives>controls, F(1.73)=4.75, p<0.03; Analysis of covariance (with age as covariate): hyperactives=controls 24 months Growth: medicated=controls; medicated=nonmedicated Body composition: medicated=controls, but group-by-time interaction on percent body fat (hyperactives increased, controls decreased); medicated=nonmedicated

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
McNutt 1976a (preliminary report) McNutt 1976b U.S. (Fair)	Significant difference in age between medicated and controls, F(1,73)=5.83, p<0.02

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Wilens 2003; 2004; 2005 U.S. (Fair)	Open-label trial of OROS MPH, non-randomized, 12-month study in children who had used OROS MPH in previous trials and were found to be responders. Setting: 14 sites Non-comparative	All subjects except one had participated in a previous trial of OROS MPH. Eligible for inclusion were children with ADHD, aged 6-13, with normal urinalysis, hematology, and blood chemistry. Subjects who were already receiving specific behavioral interventions for ADHD on an ongoing basis were permitted to enter the study, but new behavioral interventions could not be initiated during the study. Children with mild or moderate vocal or motor tics, but not a diagnosis of Tourette's syndrome, were included. Exclusions: children with Tourette's syndrome; an ongoing seizure disorder; a psychotic disorder; clinically significant GI problems: a history of hypertension; known hypersensitivity to MPH; a coexisting condition or concurrent medication likely to interfere with MPH; females who had reached menarche.	12 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Wilens 2003; 2004; 2005 U.S. (Fair)	Methylphenidate in a once-daily, osmotic controlled-release formulation (OROS MPH) Subjects were assigned to one of 3 dosing levels of OROS MPH (18 mg, 36 mg, or 54 mg qd) based on previous treatment. Dose could be adjusted up or down in 18 mg increments during the monthly clinic visits. Doses could be reduced or discontinued on weekends or nonschool days, or on other medication holidays. Mean dose at study entry: 35 mg/day Mean dose at 12 months: 41 mg/day	Allowed, but not specified	Urinalysis, hematology, serum chemistry were performed at baseline, at 6 and 12 months. Height, weight, blood pressure, and pulse were recorded at monthly clinic visits. Adverse events were elicited by the investigator and by spontaneous report by the subjects or their parents caregivers, and assessed as to severity and possible relationship to study medication. At monthly visits, parents were asked about their child's sleep quality; whether their child had experienced tics, or whether tics had changed in severity or specificity in the previous month.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Wilens 2003; 2004; 2005 U.S. (Fair)	Mean age 9.2 83% male 86% white 5.7% black 0.7% Asian 4.4% Hispanic	NR/NR/436	143 (32.8%) withdrawn, 25 because data from one site was found to be unreliable 16 (3.7%) lost to fu 407 (93.3%) analyzed 28 (6.4%) withdrew due to AEs

Evidence Table 15. Observational studies - long-term safety

Author
Year
Country **Safety outcomes**

Wilens
2003; 2004; 2005
U.S.
(Fair)

Adverse event	N (%)	Withdrawals due to AE	Specific adverse events
Headache	102 (25.1)	1	Tics: New onset occurred in 23 (6.4%) of 359 subjects with no known history of tics.
Insomnia	60 (14.7)	5	
Appetite suppression	55 (13.5)	7	
Abdominal pain	31 (7.6)	1	
Twitching	31 (7.6)	7	Sleep: sleep quality was rated good/excellent for 71% of subjects (282/398) in month 1, and for 74% of remaining subjects (134/182) in month 12. LOCF analysis showed that 69% of subjects received a good/excellent sleep quality rating at end of study.
Aggravation reaction	10 (2.5)		
Somnolence	10 (2.5)	1	
Reaction unevaluable	9 (2.2)		
Anxiety	9 (2.2)		
Weight loss	8 (2.0)	1	
Emotional lability	8 (2.0)	1	
Hostility	8 (2.0)	2	
Nausea	7 (1.7)		
Dizziness	7 (1.7)		Vital signs: 5 developed hypertension. 1 withdrew; elevated systolic readings resolved with discontinuation.
Vomiting	6 (1.5)		
Nervousness	6 (1.5)		
Depression	6 (1.5)		
Asthenia	5 (1.2)		
Hypertension	5 (1.2)	1	Growth: Mean weight decreased by 0.1 kg over the first 3 months then increased over the remainder of the study. See table below.
Apathy	4 (1.0)		
Worsening of ADHD	NR	3	
Compulsive skin picking	NR	1	
Hallucinations	NR	1	

Growth	Baseline	Month 3	Month 6	Month 9	Month 12
Weight (kg)	34.2	34.1	34.5	35.6	36.8
Rate of change (kg/mo)	---	**-0.033**	+0.133	+0.366	+0.400
Height (cm)	137.1	138.4	139.6	140.8	142.3
Rate of change (cm/mo)	---	+0.43	+0.40	+0.40	+0.50

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Wilens 2003; 2004; 2005 U.S. (Fair)	Most children were already MPH responders prior to entry into the study, and patients with known hypersensitivity to MPH were excluded.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Gualtieri 1985 U.S. (Fair)	Open-label 3-6 month followup of MPH responders.	Subjects (n=8) who appeared to respond favorably to MPH in either a short-term efficacy study or in open clinical trials. All subjects (n=8) had initially responded with improvement in attention span, greater work efficiency, decreased feelings of restlessness and impatience, improved interpersonal relationships, and diminished temper outbursts. Two of these subjects were also narcoleptics, and in both cases MPH also led to control of sleep attacks.	3-6 months
Millichap 1977 U.S. (Fair)	Before-after Setting: Children's Memorial Hospital (Chicago)	Boys, 5 to 10 years of age, referred for pediatric neurology evaluation because of hyperactive behavior and failure to achieve the level of academic potential expected in school. Signs of minimal brain dysfunction were recognized on examination and tests of perception revealed deficits in visual and/or auditory channels despite normal intelligence.	6-26 months (mean=16 months)
Safer 1973 U.S. (Fair)	Retrospective cohort (student health records) Setting: six elementary schools in Baltimore, Maryland	Hyperactive children who received stimulant medication for >/= 2 years	≥ 2 years

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Gualtieri 1985 U.S. (Fair)	MPH was administered in doses ranging from 0.1 to 2.0 mg/kg, bid or tid. Most subjects received doses below 0.5 mg/kg and only the 2 narcoleptic subjects received doses in excess of that level.	Not reported	Monthly clinic visits, NOS.
Millichap 1977 U.S. (Fair)	MPH was prescribed as an adjunct to remedial education, beginning with a dose of 5 mg, morning and noon on school days only and increasing the dose to a maximum of 20 mg daily when necessary	NR	Measurements of height and weight were made by the author at the times of initial neurologic examination and at re-examination during treatment
Safer 1973 U.S. (Fair)	DEX MPH Unmedicated controls Mean dosages NR	NR	School nurses completed a form based on review of school health records

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Gualtieri 1985 U.S. (Fair)	Mean age 27.2 100% male Ethnicity NR (represents n=22, of which 8 were included in the long-term followup study)	NR/NR/8	3 withdrew Lost to fu NR 0 analyzed (results described per individual)
Millichap 1977 U.S. (Fair)	Mean age nr 100% male Race NR	NR/NR/36	NR NR NR
Safer 1973 U.S. (Fair)	Mean age nr 89.8% male in children on medication; 100% male in unmedicated control group 100% white	NR/NR/44 on medication, 14 unmedicated controls	NR NR 44 on medication (DEX=29, MPH=20), 14 unmedicated controls

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Gualtieri 1985 U.S. (Fair)	One subject consumed a month's supply of MPH in "an abortive suicide attempt".
Millichap 1977 U.S. (Fair)	Patients that lost weight: 2/36 (5.5%) Heights (% patients at baseline/after therapy) (difference NS) Above 50th percentile: 14 (38.9%) / 13 (36%) Below the 50th percentile: 22 (61.1%) / 23 (64%) Below the 5th percentile: 4 (11.1%) / 0 Decrease rate of growth: 2 (5.5%)
Safer 1973 U.S. (Fair)	DEX; MPH: high-dose (> 20 mg), all, low-dose (≤ 20 mg); controls Percentile changes in: Weight: -20.38; -10.0, -6.35, -2.7, +6.79 DEX > all MPH dosage groups and controls; MPH high-dose and all doses > controls; MPH low-dose=controls Height: -13.45; -9.40, -5.20, -1.00; +1.29 DEX > MPH all-dosage, low-dosage and control groups, but DEX=MPH high-dosage group; MPH high-dosage > controls; MPH all-dosage and low-dosage=controls All differences remained significant following a covariance analysis that controlled for differences in initial values of weight and height percentiles

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Gualtieri 1985 U.S. (Fair)	
Millichap 1977 U.S. (Fair)	
Safer 1973 U.S. (Fair)	Initial weight/height percentile values were initially larger for DEX group

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Zeiner 1995 Norway (Fair)	Prospective cohort study Setting: Child psychiatric outpatient unit	Boys, between the ages of 7-12 years, DSM-III diagnosis of ADHD	Mean=634 days
Safer 1975 (Poor)	Prospective cohort study setting: NR	only children who remained in the school for one calendar year were included in the evaluation. Those children whose therapy was changed from one stimulant medication to another during the calendar year, or was discontinued during the school year, were also excluded	I year
McGough 2005 U.S.	Multicenter Long-term follow-up of two different placebo-controlled trials of Adderall (Biederman 2002 and McCracken 2003).	Boys and girls aged 6-12 years, mostly with combined subtype, with vital signs in the normal range, who satisfied DSM-IV criteria for a primary diagnosis of ADHD. Patients had to complete their previous trial without any clinical relevant adverse events (AEs) or withdrew from the previous trials for reasons other than AEs.	24 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Zeiner 1995 Norway (Fair)	Medicated (MPH 23 mg) vs unmedicated	Medicated: no cc meds Unmedicated: 3 (13%) on imipramine x 6 weeks; 1 (4%) on imipramine x 6 months	measurements for height, weight, heartrate and blood pressure.
Safer 1975 (Poor)	MPH: 27mg/day, range 10-60mg dextroamphetamine 12mg/day, range 5-20mg	NR	the height and the weight were recorded by two independent examiners
McGough 2005 U.S.	Adderall XR (Mixed Amphetamine Salts) Starting dose was 10 mg/d and could be uptitrated by 10 mg increments to 20 or 30 mg/d.	Prohibited concomitant medications included: alpha-2 agonists, anticonvulsant drugs, and medications that affect blood pressure, heart rate, or central nervous system performance.	Safety was assessed by analysis of AEs and vital signs recorded at each study visit, height and weight at baseline and months 12-24, lab tests conducted at baseline and 6-month intervals, physical examinations performed at baseline and months 12, 18, and 24. AEs were collected by spontaneous report and by investigator queries of subject and caregiver at each visit.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Zeiner 1995 Norway (Fair)	mean age 9.0 yrs 100% male Ethnicity NR	36/25/23	0/0/23 analyzed
Safer 1975 (Poor)	Mean age: 10.3 years, range 8-13 years Gender: 80% male 100% Caucasian	66/NR/NR	NR/NR/26
McGough 2005 U.S.	Mean age: 8.7 years 78% male 73% white 12% Black 9% Hispanic 1% Asian/ Pacific Islander 3% Other	NR / 635 / 568	284 total (87 of these formally "withdrew consent") 74 273 (48%) completed study

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Zeiner 1995 Norway (Fair)	Measurements at end of treatment: Medicated (n=23) vs unmedicated (n=23) Weight: 42.0 vs 40.3; p=NS Height: 150.4 vs 148.3; p=NS
Safer 1975 (Poor)	Compare growth rate in school year and summner Continued group (CG): growth rate of the height and weight, NS Discontinued group (DG): dextroamphetamine, weight- school year<summer, p<0.005 dextroamphetamine, height- school year< summer, p<0.05 MPH, weight- school year<summer, p<0.005 MPH, height- school year< summer, p<0.05
McGough 2005 U.S.	92% (n=525) of patients had ≥ 1 AE during the study. Of patients reporting AEs, 84% (n=440) experienced at least 1 AE deemed by the investigator to be "possibly" treatment related. Most frequently reported AEs: headache (15% of all AEs), anorexia (15% of all AEs), and insomnia (11% of all AEs). 21 serious AEs (SAEs) were reported by 18 patients (3%); only 2 (both convulsions) were thought to be related to Adderall; both were discontinued from the study. 12 SAEs were severe, but none were thought to be related to Adderall. 84 patients (15%) withdrew due to AEs; the most frequently reported AEs associated with treatment withdrawal included weight loss (n=27), anorexia/decreased appetite (n=22), insomnia (n=11), depression (n=7), and emotional lability (n=4). Overall medication compliance was 94%. Mean systolic blood pressue increased by 3.5 mmHg, diastolic blood pressure increased by 2.6 mmHg, and mean puse increased by 3.4 beats/min. 134 reports of weight loss occurred over the 24 months. The decrease in the expected weight gain was -7.8 kg for the patients above the 75th percentile on the CDC weight charts at baseline, and was -2.1kg for patients below the 25th percentile at baseline.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Zeiner 1995 Norway (Fair)	
Safer 1975 (Poor)	
McGough 2005 U.S.	635 patients were enrolled in the original PCTs; 568 enrolled from those studies into this long-term extension.

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Wilens 2005/Spencer 2006 U.S.	Open-label extension study Setting: Multicenter, 14 sites	Children with ADHD who all (except one) participated in one of several previous efficacy or pharmacokinetic studies	24 months
Batterson 2005	Cross-sectional study Setting: NR	MPH IR group: Children who had taken MPH IR for a minimum of 2 years at a minimum dose of 20 mg/day; no missing permanent mandibular teeth (with the exception of third molars); excellent diagnostic quality of panoramic radiograph; no prior comprehensive orthodontic treatment; absence of any disorder affecting growth and/or tooth development; no history of ingesting any medication affecting growth and/or tooth development Healthy control group: Matched for gender and age within 1 month; inclusion criteria identical to MPH IR group, with exception of having no history of any MPH IR use and no history of any long-term medication use	N/A
Charach 2006	Open-label extension study Participants drawn from referrals to an assessment and treatment program for ADHD	Confirmed DSM-III-R diagnosis of ADHD based on parent and teacher interviews; aged 6-12 years; completion of a 12-month RCT of combined MPH IR and parent-treatment	5 years

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Wilens 2005/Spencer 2006 U.S.	MPH; OROS® (for growth analysis: mean daily dose increased from 34.3 mg at baseline to 43.7 mg at month 21)	NR	Height and weight measured monthly during the first year and every 3 months thereafter at clinic visits
Batterson 2005	MPH IR at a minimum dose of 20 mg/day	NR	Assessment of dental age using panoramic radiograph
Charach 2006	Psychostimulants (% patients): 43 (54%) DEX IR: 19% MPH IR: 81% Dosages NR	NR	Standing height: measured in centimeters without shoes from floor to vertext of head Weight: in indoor clothing, without shoes, measured in kilograms Both measured annually using an Accustat Genentec stadiometer

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Wilens 2005/Spencer 2006 U.S.	Growth analysis only: Mean age 9.4 years (6-13) 83.7% male 87.1% White 5.6% Black 0.6% Asian 2.8% Hispanic 3.9% other	NR/NR/407	178 (43.7%) total withdrawn 31 (7.6%) withdrawn AE 29 lost to fu 178 analyzed (had height and weight measured at both baseline and 21 months)
Batterson 2005	Mean age: 11.6 years 71% male Race NR	NR/NR/84	N/A
Charach 2006	Demographics NR	91/91/79	14% withdrawn/LTFU NR/height=45 (49%) and weight=45 (49%)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Wilens 2005/Spencer 2006 U.S.	Height was on average 0.23 cm less than expected at 21 months Weight was on average 1.23 kg less than expected at month 21, weight did not increase and BMI decreased slightly in the first 4 months Drug holidays did not significantly affect growth
Batterson 2005	MPH IR vs control Dental age (years): 12.20 vs 12.58, NS
Charach 2006	Association between increased dose and height (controlled for time since initiation of treatment): ß coefficient = -0.11, p<0.001 Association between increased dose and weight (controlled for time since initiation of treatment): ß coefficient = -0.29, p<0.001

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Wilens 2005/Spencer 2006 U.S.	Growth analyzed in a subgroup of study subjects
Batterson 2005	
Charach 2006	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Pliszka 2006	Cohort, retrospective Data source: University-based child and adolescent psychiatry/psychopharmacology clinical database	Diagnosis of ADHD; ≥ 1 years of continuous treatment with a single class of stimulants medication (MPH or MAS) and not switched from one stimulant to another at any point during the treatment period; no treatment with any other psychotropic medication	Mean=2.6 years
Forrester 2006	Cross-sectional study Data source: Texas Poison Control Network (TPCN)	Cases were all calls involving MPH IR received during 1998-2004	Annual

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Pliszka 2006	MPH (any form) vs MAS (any form) Highest daily dosages: 34.8 mg vs 22.7 mg	NR	Height and weight measured at least 3 times per year using the same scale throughout the study period; always recorded within 4 months of the last medication refill; Growth Plus 3.1 program (Applied Micro Solutions) calculated Z scores according to the child's age and gender using normative data from the national Center for Health Statistics
Forrester 2006	MPH IR dosage NR	NR	Medical outcome rated as no effect (no symptoms due to exposure), minor effect (some minimally troublesome symptoms), moderate effect (more pronounced, prolonged symptoms), major effect (symptoms that are life-threatening or produce significant disability or disfigurement) or death

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Pliszka 2006	Mean age=8.7 years 81.0% male Race NR	NR/NR/179	NR/NR/63 (35%) included in 3-year analysis
Forrester 2006	Age (years): < 13: 20.3% 13-19: 54.7% > 19: 25% 61.9% male Race NR	Calls: 6798 total/eligible NR/enrolled=322	Withdrawn N/A/Medical outcome unknown for 133 MPH IR abuse calls (41%)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Pliszka 2006	Final Z scores for MAS vs MPH: Height: 0.0 vs -0.2 Weight: 0.4 vs 0.6 BMI: 20.1 vs 20.9 No main effects for either stimulant type on height, weight or BMI
Forrester 2006	Medical outcomes: All MPH IR exposures vs **MPH IR abuse exposures** vs MPH IR nonabuse exposures: No effect: 49.9% vs **28.6%** vs 52.1% Minor effect: 28.5% vs **36.5%** vs 27.7% Moderate effect: 19.2% vs **29.1%** vs 18.2% Major effect: 2.4% vs **5.8%** vs 2.0% Death: 0 vs **0** vs 0 Proportion of annual human abuse calls relating to MPH IR: 1998: 10.6% 1999: 11.4% 2000: 7.2% 2001: 5.9% 2002: 7.4% 2003: 9.8% 2004: 7.3% Total: 8.5%

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Pliszka 2006	
Forrester 2006	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Elementary School Children - Stimulants (combined therapy)			
Rao 1998 U.S./Canada (Fair)	Cohort, retrospective Setting: National Cooperative Growth Study (NCGS) Database	1) diagnosis of IGHD or ISS (max stimulated GH level < 10 µg/L for IGHD and ≥ 10 µg/L for ISS); 2) no GH therapy before enrollment; 3) prepubertal at enrollment; 4) between 3 and 20 years of age at enrollment; 5) height below the 5th percentile for age and sex; 6) no other significant medical conditions that affect growth; and 7) height reported after at least 180 of GH therapy. Patients who met the criteria and who also were treated for ADHD with MPH or pemoline	NR
Weizman 1987 Israel (Fair)	Before-after, prospective Setting: NR	**Patients:** ADDH and (1) regular attendance at school, (2) cooperative parents and teacher willing to fill out the Conners rating scale, (3) IQ > 80; (4) absence of significant medical or neurological disease; (5) all patients were drug free for at least 3 months **Controls:** No psychopathology was observed in the subjects or their pareitns. All subjects were free of lifetime psychiatric disorder	9 weeks
Elementary School Children - Mixed amphetamine salts			

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Elementary School Children - Stimulants (combined therapy)			
Rao 1998 U.S./Canada (Fair)	MPH or pemoline Mean dosages NR	NR	Information from case report forms
Weizman 1987 Israel (Fair)	MPH 10.3 mg	NR	Blood samples for GH were obtained at 8:00-9:00 am after an overnight fast as follows: (1) morning before treatment initiation; (2) 2 hours after first dose; (3) after 4 weeks; (4) 2 hours after repeated challenge with MPH 5 mg Plasma GH levels were determined by double antibody RIA using materials provided by SORIN S.P.A. (France)
Elementary School Children - Mixed amphetamine salts			

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Elementary School Children - Stimulants (combined therapy)			
Rao 1998 U.S./Canada (Fair)	Mean age=9.3 years 74.8% male Race NR	NR NR 3897 enrolled	n/a n/a Analyzed: IGHD-ADHD=184; IGHD=2313; ISS-ADHD=117; ISS=1283
Weizman 1987 Israel (Fair)	Mean age=8.8 years 81% male Race NR	NR NR 16 patients/16 controls	NR NR 16 patients/16 controls
Elementary School Children - Mixed amphetamine salts			

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Elementary School Children - Stimulants (combined therapy)	
Rao 1998 U.S./Canada (Fair)	Factors w/significant effect on GH-therapy response (stepwise multiple regression): MPH/pemoline-treatment: Regression-coefficient= -0.17; contribution to R 2= 0.002; p=0.001
Weizman 1987 Israel (Fair)	GH (ng/ml) in ADDH patients Pre-treatment: 0': 2.6, p=NS 120': 5.9, p=NS Post-treatment: 0': 2.1; p=NS 120': 7.8; p=p<0.05 GH in controls: NR
Elementary School Children - Mixed amphetamine salts	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Elementary School Children - Stimulants (combined therapy)	
Rao 1998 U.S./Canada (Fair)	
Weizman 1987 Israel (Fair)	
Elementary School Children - Mixed amphetamine salts	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Wilens 2005 U.S.	Open-label extension study Setting: Multicenter	DSM-IV criteria for ADHD, adolescents who were part of the previous study	6 months
Connor 2005			
Donner 2007			
Findling 2005 U.S.	Open-label extension study Setting: multicenter	DSM-IV criteria for ADHD, children who were part of one of two previous studies, no clinically relevant AEs from prior study	2 years
Spencer 2005 U.S.	Open-label extension study Setting: multicenter	DSM-IV criteria for ADHD, adolescents who participated and completed the previous study and those who discontinued early so long as treatment was not interrupted, excluded patients from previous study who discontinued due to noncompliance or safety concerns	6 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Wilens 2005 U.S.	MAS XR flexible dosing 10-60 mg/day (mean dose ranged 29 mg/day at 1 month to 32 mg/day at 4 months, >80% subjects received 20-40 mg/day for the study duration)	Prohibited medications (not including ADHD medications) that could affect blood pressure or heart rate	Sitting blood pressure and pulse at baseline, weekly during the first month, then monthly for up to 6 months clinic visits ECG measurements at baseline, month 3, and month 6 or the final clinic visit; central lab used to evaulate all ECG readings
Connor 2005			
Donner 2007			
Findling 2005 U.S.	MAS XR; Adderall XR® (mean dose ranged from 20 mg/day at 3 months to 22 mg/day at 24 months)	Prohibited concomitant medications included: anticonvulsant drugs, clonidine, guanfacine, and any medications that may have affected blood pressure, pulse, or central nervous system performance	Resting sitting blood pressure and pulse at baseline, weekly for first month, then monthly up to 24 months clinic visits; ECG measurements at baseline, 12, 18, and 24 months clinic visits
Spencer 2005 U.S.	MAS XR, flexible dosing 10-60 mg/day, most patients (>80%) received 20-40 mg/day throughout the study	Prohibited medications (not including ADHD medications) that could affect blood pressure or heart rate	Weekly study visits for the first 4 weeks, then visits 30 days apart up to 6 months, followup telephone contact at ~ 30 days post discontinuation or after study completion to collect AE information Body weight measured at each study visit

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Wilens 2005 U.S.	Mean age 14.4 years (13-17) 71.0% male 72.0% White	NR/NR/138	28 (20%) withdrawn by 6 months 110 analyzed at 6 months
Connor 2005			
Donner 2007			
Findling 2005 U.S.	Mean age 8.7 years (6-12) 78% male 73% White 12% Black 9% Hispanic 4% other	NR/NR/568	291 (51%) withdrawn by 24 months 277 analyzed at 24 months
Spencer 2005 U.S.	Mean age 14.4 years (13-17) 71.0% male 71.7% White 15.2% Black 10.1% Hispanic 2.8% other	NR/NR/138	33 (23.9%) total withdrawn 6 (4.3%) withdrawn AE 19 (13.8%) withdrawn due to protocol violations and lost to fu 105 analyzed at 6 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Wilens 2005 U.S.	1 (0.7%) tachycardia (124 bpm), MAS XR dose NR 1 (0.7%) pulse 115 bpm at 5 months, MAS XR 30 mg/day 2 (1.4%) postural hypotension, MAS XR dose NR 2 (1.4%) syncope, MAS XR dose NR Decrease in QTcB interval from baseline (-4.6±19.9 msec) was statistically (p=.009), but not clinically, significant at 6 months
Connor 2005	
Donner 2007	
Findling 2005 U.S.	4 (0.7%) cardiovascular AEs: 1 (0.2%) tachycardia (108 bpm at baseline, 101 to 121 bpm long-term treatment), moderate in severity, MAS XR 20 mg/day 2 (0.4%) intermittent chest pain that resolved, mild in severity, MAS XR 20 mg/day (1 at 9 months, 1 at 12 months) 1 (0.2%) hypertension, 130/90 mm Hg after 12 months, moderate severity, MAS XR 10 mg/day Change in group mean QTcB values NS Most common ECG abnormalities, none clinically significant, at MAS XR 20 mg/day, were: 25 (4.4%) sinus arrhythmia 5 (0.9%) ST-T wave abnormalities 4 (0.7%) poor anterior R-wave progression
Spencer 2005 U.S.	34 (24.6%) anorexia, MAS XR dose 10 mg n=8, 20mg n=10, 30 mg n=13, 40 mg n=3, 50 mg n=1, 60 mg n=2 34 (24.6%) weight loss, 2 patients discontinued treatment, MAS XR dose 10 mg n=3, 20 mg n=12, 30 mg n=15, 40 mg n=3, 50 mg n=2, 60 mg n=0 Mean body weight decreased by 2.4 kg (5.2 lbs) from baseline to endpoint, p<.0001 Decrease in body weight among MAS XR-naïve patients (-9.2 lbs, p<.0001) was greater than among MAS XR-continuous patients (-3.3 lbs, p=.0004) Magnitude of weight loss related to baseline weight, those >75th percentile at baseline lost the most weight (4.2 kg [9.2 lbs], p<.0001)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Wilens 2005 U.S.	
Connor 2005	
Donner 2007	
Findling 2005 U.S.	
Spencer 2005 U.S.	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Faraone 2005 U.S.	Open-label extension study Setting: multicenter	DSM-IV criteria for ADHD, children exposed to double-blind study medication or not due to enrollment termination from one of two previous studies, children who discontinued previous study completed at least 1 week of double-blind treatment and had no clinically significant adverse medical experiences	6-30 months
Adults			
Alder 2005 U.S./Canada	Interim analysis of open-label extension study Setting: multicenter, 31 sites	DSM-IV criteria for ADHD, adults who were part of one of two previous studies, no selection based on completion of previous study or responders	97 weeks
Horrigan 2000 U.S. (Fair)	Before-after, retrospective Setting: University-based neuropsychiatric clinic	Adult outpatients with ADHD (DSM-IV 314.01, combined type)	12 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Faraone 2005 U.S.	MAS XR 10-30 mg/day (mean dose NR)	NR	Weekly visits for the first 4 weeks then monthly thereafter Baseline value was the value immediately prior to any MAS XR dose in a treatment study Endpoint was the last height value recorded
Adults			
Alder 2005 U.S./Canada	Atomoxetine, maximum total daily dose did not exceed 160 mg/day (mean final dose=98.6 mg/day, median final dose=120 mg/day)	NR	Every other week for the 1st 4 visits, monthly for 4 visits, then every 3 months for duration of study Adverse events assessed by open-ended questioning at each visit and lab tests ECG completed w/in 30 days of 1st visit - baseline measurement
Horrigan 2000 U.S. (Fair)	Adderall (modal dose 10 mg - bid dosing)	SSRI (sertraline or venlafaxine) in 4 patients	Motor tic

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Faraone 2005 U.S.	Mean age 8.7 years (6-12) 78% male 73% White 12% Black 9% Hispanic 19% Asian/Pacific Islander 3% other	NR/638/568	Height >24-30 months, 203 analyzed Weight >24-30 months, 199 analyzed BMI >24-30 months, 198 analyzed
Adults			
Alder 2005 U.S./Canada	Mean age=42.4 years 64.1% male 92.2% White 3.6 % Hispanic 2.1 % African American 1.0% Eastern Asian 0.5% Western Asian 0.5% other	NR/536/385	260 (67.5%) total withdrawn 42 (10.9%) withdrawn AE 110 lost to fu 125 continued after 97 weeks
Horrigan 2000 U.S. (Fair)	Mean age=33 50% male Ethnicity NR	NR/NR/24	NR NR 24

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Faraone 2005 U.S.	Growth was less than expected based on CDC norms Losses in expected weight and BMI were greatest for heaviest children, losses in expected height were greatest for tallest children Nearly all growth deficits occurred in year one; loss in expected growth NS in year 2 Those previously treated with stimulants showed smaller weight and height deficits for the first year
Adults	
Alder 2005 U.S./Canada	Mean decrease in weight of 1.3 kg, p<.001 Increases in heart rate, mean change 5.1 bpm, p<.001 Increases in blood pressure, mean change for systolic and diastolic <2.0 mm Hg, p<.05 No clinically relevant changes in QTc (Fridericia) No clinically significant changes in lab measures
Horrigan 2000 U.S. (Fair)	Motor tic: 1/24 (4%)

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Faraone 2005 U.S.	
Adults	
Alder 2005 U.S./Canada	35 (9.1%) of patients rolled into the open-label trial w/out entering the discontinuation period of the previous studies
Horrigan 2000 U.S. (Fair)	

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Weisler 2005 U.S.	Open-label extension study Setting: multicenter	DSM-IV criteria for ADHD, healthy adults at short-term study entry who completed at least 1 week of treatment without experiencing any clinically important AEs in the short-term study, excluded those with blood pressure consistently >139/89 mm Hg, heart rate consistently <50 or >120 bpm	24 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Weisler 2005 U.S.	MAS XR; Adderall XR®, 20-60 mg/day, after 1 month 179 (80.3%) = dose of 40 or 60 mg/day (mean dose NR)	Prohibited medications that could affect heart rate, blood presssure, or CNS	Resting sitting blood pressure and pulse at baseline, weekly for the 1st 4 weeks, then monthly up to 24 months ECG at baseline, at months 3, 6, 12, 18, and 24 or upon early termination Central lab used to evaluate ECGs

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Weisler 2005 U.S.	Mean age=39.8 years (18-76) 59.3% male 90.5% White 5.0% Hispanic 2.7% Black 1.8% other	NR/NR/223	147 (66%) total withdrawn 48 (22%) withdrawn AE 23 lost to fu 76 analyzed at 24 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Weisler 2005 U.S.	7 (3.1%) discontinued due to a cardiovascular AE: 5 (2.2%) hypertension; MAS XR 20 mg/day, n=1; 40 mg/day, n=1; 60 mg/day, n=3 2 (0.9%) palpitations and/or tachycardia, MAS XR 40 mg/day, which resolved upon discontinuation Clinically insignificant increases in mean QTcB (corrected by Bazett's formula) (7.2 msec, p<.001) and QTcF intervals (2.9 msec, p=.009) at 24 months No subject exhibited QTcB interval >480 msec (QTcF [corrected by Fridericia's formula] >454 msec) 2 (0.9%) clinically significant abnormal ECGs; n=1 at baseline, abnormal T-wave and lengthened QT interval that resolved, n=1 left anterior hemiblock at month 3 and ongoing at month 24; neither subject withdrawn

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Weisler 2005 U.S.	Rollover from short-term study divided into 3 groups for analysis: MAS XR naïve, MAS XR continuous, and MAS XR interrupted

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Design	Eligibility criteria	Duration
Preschool children			
Ghuman 2001 U.S. (Fair)	Retrospective cohort (chart review) Setting: Kennedy Krieger Institute (KKI) Infant and Preschool Psychiatry Clinic (IPC)	(1) a DSM-IV diagnosis of ADHD; (2) psychostimulant treatment initiated between the ages of 3 and 5 years; (3) chart documentation of clinical status both before and during psychostimulant treatment; and (4) follow-up completed for 24 months	24 months

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Interventions (mean dose)	Concomitant medication	Safety Assessment
Preschool children			
Ghuman 2001 U.S. (Fair)	Mean dosages at 3-, 12- and 24-months: MPH: 11.65, 20.8, and 26.67 mg Amphetamine (DEX or Adderall): 7.5, 15.4 and 2.5 mg	Psychotropic medications (unspecified) for mood disorders, anxiety disorders, and obsessive-compulsive disorder	Clinic notes of Side Effects Rating Form (SERF) ratings

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to follow-up Analyzed
Preschool children			
Ghuman 2001 U.S. (Fair)	Mean age=4.7 years 85.2% male 52% white 48% black	71/27/27	6 (22.2%) withdrawn 0 lost to fu Analyzed: 12 months=23, 24 months=21

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Safety outcomes
Preschool children	
Ghuman 2001 U.S. (Fair)	Development of de novo tics/worsening of preexisting tics: none *Average weight gain (mean/expected/percentil)* Month 3 (n=25): 0.6 kg/0.6 kg/nr Month 12 (n=20): 0.6 kg/2.0/75th Month 24 (n=14): 2.6 kg/5.0/75th *Average height gain (mean) (all as expected):* Month 3 (n=17): 1.8 cm Month 12 (n=18): 5.6 cm Month 24 (n=12): 11.4 cm

Evidence Table 15. Observational studies - long-term safety

Author Year Country	Comments
Preschool children	
Ghuman 2001 U.S. (Fair)	

Evidence Table 16. Quality of observational studies of long-term safety

Author	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Brehaut 2003	Yes	Yes	Yes	Yes	Yes
Gadow 1999	Yes	Yes	No	Yes	Yes
Ghuman 2001	No	Unclear	No	No	Unclear
Gross 1976	No	Yes	Yes	Yes	Yes
Gualtieri 1985	No	Yes	No	No	Unclear
Horrigan 2000	Yes	Yes	No	No	Unclear
Kratochvil 2001	Yes	Yes	No	No	Yes
Mattes 1983	No	No	Yes	No	Yes
McNutt 1976a (preliminary report) McNutt 1976b	Unclear; # of children in short-term studies NR	Unclear	Yes	Yes	Yes
Millichap 1977	Yes	NR	Yes	No	Yes

Evidence Table 16. Quality of observational studies of long-term safety

Author	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality	Notes
Brehaut 2003	Yes	Yes	Fair	
Gadow 1999	Yes	Yes	Fair	
Ghuman 2001	Yes	Yes	Fair-Poor	
Gross 1976	NR	Yes	Fair	Study included only patients within the investigator's clinical practice, for whom pre-treatment weight and height data were available.
Gualtieri 1985	NR	Yes	Fair	
Horrigan 2000	NR	Yes	Fair	
Kratochvil 2001	Yes	No	Fair	
Mattes 1983	Yes	Yes	Fair	
McNutt 1976a (preliminary report) McNutt 1976b	Yes	Yes	Fair	
Millichap 1977	No	Yes	Fair	

Evidence Table 16. Quality of observational studies of long-term safety

Author	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Quinn 1975	No	Yes	No	No	Yes
Rao 1998	Yes	n/a	Yes	No	Yes
Safer 1973	Yes	Yes	No	Yes	No
Safer 1975	Yes	Yes	Yes	No	Unclear
Safer 1972	No	Yes	Yes	No	No
Satterfield 1979	Yes	Yes	Yes	Yes	Yes
Weizman 1987	Unclear	Unclear	Yes	Yes	Yes
Wernicke 2003	No	Yes	Yes	Yes	Yes for ECG; unclear for adverse events
Wilens 2003; 2004;	No	Yes	Yes	Yes	Yes
Zeiner 1995	No	Yes	Yes	No	Unclear

Evidence Table 16. Quality of observational studies of long-term safety

Author	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall adverse event assessment quality	Notes
Quinn 1975	NR	Yes	Fair	
Rao 1998	Yes	Unclear	Fair	
Safer 1973	Yes	Yes	Fair	
Safer 1975	No	Yes	Poor	
Safer 1972	NR	Yes	Fair	Main outcome (percentile change) uses two timepoints (single baseline measurement taken at school admission at age 5-6, to end of 2+ year treatment) rather than construction of individual growth curves. Classification of treatment during summer based on child's self-report, rather than prescription records.
Satterfield 1979	NR	Yes	Good	Adherence was assessed by monthly urinalysis.
Weizman 1987	No	No	Fair	
Wernicke 2003	Unclear	Yes	Fair	
Wilens 2003; 2004; [illegible]	NR	Yes	Fair	Study selected for MPH responders, decreasing likelihood of AEs.
Zeiner 1995	Yes	Yes	Fair	

Evidence Table 17. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Oesterheld 1998	RCT cross-over in residential school	Native american child 5 to 12 years with full or partial fetal alcohol syndrome with ADHD	Fetal alcohol syndrome (full or partial) with ADHD
MacDonald/Fredericks 2005	Observational	Children 10-14 years with established ADHD taking methylphenidate	No

Evidence Table 17. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout period	Allowed other medications/ interventions
Oesterheld 1998	Methylphenidate 0.6 mg /kg 5 days- lactose placebo 5 days and viamin C placebo 2 days off in between Total 3 weeks	NR	None
MacDonald/Frederi cks 2005			

Evidence Table 17. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Oesterheld 1998	Conners Parent Rating Scale (CPRS-48), and the Conners Teacher Rating Scale (CTRS-39) daily during active treatment	Mean age=8.25 yrs Gender: 50% male Ethnicity: 100% Native American
MacDonald/Fredericks 2005	Reinforcing effects were assessed using a double-blind choice procedure, with six sampling sessions and six choice sessions. Participant-rated effects were measured using self-report questionnaires. Clinical effects were measured using direct observations and behavior ratings.	Mean age=12 yrs Gender: 80% male Ethnicity: NR

Evidence Table 17. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Other population characteristics (mean scores)		Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Oesterheld 1998	2 boys full FAS	2 girls partial FAS	Screened: 30 Eligible: 7 Enrolled: 4	NA
MacDonald/Fredericks 2005			Screened: 14 Eligible: 5 Enrolled: 5	0/ 0/ 5

Evidence Table 17. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Results
Oesterheld 1998	CPRS-48 Hyperactivity-Impulsivity scale (HI) F= 4.34 df 4 P< 0.05 the daydreaming attention scale was NS CTRS-39 HI F= 6.42 df 4 P < 0.02
MacDonald/Frederi cks 2005	Differences between the number of MPH, Placebo, and Neither choices across participants were significant ($X^2 = 9.6$; $p < 0.01$). Three of five participants reliably chose MPH more often than placebo. MPH produced idiosyncratic patterns of participant-rated effects but failed to produce significant clinical effects.

Evidence Table 17. Placebo-controlled trials in preschool children and adolescents

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Oesterheld 1998	NR	During active treatment- **Decreased appetite** 75% **Stomach ache** 50% **Headache** 50%	Total 0 Due to AEs 0	
MacDonald/Fredericks 2005	NR	NR	NR	

Evidence Table 18. Quality of abuse - diversion

	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?**	**Reporting of attrition, crossovers, adherence, and contamination**
Oesterheld 1998	NR	Unclear	Y; only 4 participants	Y	Y	Y	Y	n/a
Fredericks 2005	Y; The order in which placebo and MPH were scheduled in the sampling sessions was counterbalanced across subjects and within-subjects across weeks.	Y	Y; only 5 participants	Y	Y	Y; medication dispensers blinded	Y	n/a

Evidence Table 18. Quality of abuse - diversion

					External Validity	
Author, Year Country	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/eligible/enrolled**	**Exclusion criteria**
Oesterheld 1998	N/N	NR	N	Poor; not sure how to rate this study	30/7/4	Pregnant, evidence of lactose intolerance, prior psychotropic medication use, or acute and chronic medical or neurologic disorders (including current history of seizures or lead levels of more than 9 mcg/dL). Height and weight at or below the 3rd percentile. IQ < 60.
Fredericks 2005	N/N	NR	N	Poor; not sure how to rate this study	14/5/5	Taking any other type of psychoactive medication, exhibited any gross neurological, sensory, or motor impairment, had a history of other significant learning or psychiatric problems, and/or had a known family history of diabetes.

Evidence Table 18. Quality of abuse - diversion

Author, Year Country	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Oesterheld 1998	NR/Y Study drug given M-F/no drug given Sat/Sun; no tx drugs given for 2 days between tx trials. [Methylphenidate half-life 2.6 h]	Y	n/a	U of South Dakota: USF-Minigrant 94 202-4590-005	limited; small N; lack of standardized tests
Fredericks 2005	n/a	N; All participants were taking their maintenance dose of MPH at noon on experimental days.	n/a	NR	Limited; small N, simulated class room environment