Drug Class Review
on
Pharmacologic Treatments for ADHD

Final Report

Addendum: Evidence Tables

August 2005

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 chidren			
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

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 chidren			
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

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 chidren		
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

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
Preschool chidren			
Schleifer 1975 (Fair)	Mean IQ=102 (86-124) Hollingshead scale (socioeconomic class): Mean=2.5	NR/NR/28	0/2/26
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

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

Author Year (Quality)	Results
Preschool chidren	
Schleifer 1975 (Fair)	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)	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

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 chidren				
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	

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

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
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
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
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
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

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

Author Year (Quality)	Results
Musten 1997 Firestone 1998 (Fair)	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
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

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

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

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
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

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

Author Year (Quality)	Results
Conners 1975 (Poor)	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

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	

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

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Adolescents			
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			
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		
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
Adolescents			
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
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

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

Author Year (Quality)	Results
Adolescents	
Brown 1988 (Fair)	*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)	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				
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

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

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

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
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
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

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

Author Year (Quality)	Results
Varley 1983 (Fair)	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	Parent rating (mean dose), placebo: methylphenidate
Coons 1986 (Fair)	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

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	

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

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
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
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
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
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

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

Author Year (Quality)	Results
Smith 1998 Evans 2001 (Fair)	**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
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

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

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

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
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

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

Author Year (Quality)	Results
Klorman 1990 Klorman 1991 Klorman 1992 (Fair)	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

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	

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

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Bostic 2000 (Fair)	DB, randomized, crossover	adolescents diagnosed with ADHD.	comorbidity: mean number of subjects school problems repeated grade: 7 special education services: 10 comorbid disorders (lifetime) major depressive disorder: 7 any anxiety disorder: 8 >2 anxiety disorders: 4 oppositional defiant disorder: 12 conduct disorder: 4 smoking: 4 tic disorders: 2 eneuresis: 3 Prior ADHD treatment Methylphenidate: 6 Amphetamine: 4 Tricyclic antidepressants: 4 Clonidine: 1

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
Bostic 2000 (Fair)	pemoline dosed twice daily (morning and after school), week 1: increased 1mg/kg/day week 2: increased 2mg/kg/day week 3: increased 3mg/kg/day or placebo. Mean dose at week 3= 150.6 mg	10 week study period. Washout required of at least 2 weeks of all psychotropics before study. 2 treatment periods lasting 4 weeks, separated by 2 week washout periods.	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
Bostic 2000 (Fair)	DSM-IV derived ADHD scale, at end of each treatment arm.	mean age: 14 yrs males: 86% caucasian: 90%

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
Bostic 2000 (Fair)	previous diagnosis of ADHD with meds: 43% previously treated with at least 1 stimulant: 7% previously treated with 2 stimulants: 23% previously treated with tricyclic antidepressants: 9% moderate ADHD: 57% severe ADHD: 14%	32 screened/ 22 eligible/ 21 enrolled	0 withdrawn/4 lost to follow/ 21 analyzed

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

Author Year (Quality)	Results
Bostic 2000 (Fair)	**ADHD Rating Scale** **symptom cluster: mean score pemoline vs mean score placebo; p-value** Hyperactivity (DSM-IV): 9.5 vs 12.68; 0.040 difficulty remaining seated: 1.15 vs 1.89; 0.009 is fidgety: 1.80 vs 2.53; 0.028 has difficulty playing quietly: 1.40 vs 1.95; 0.002 talks excessively: 1.80 vs 2.05; 0.008 feels on the go: 1.75 vs 2.00; 0.673 Inattentiveness (DSM-IV) shifts activities: 1.70 vs 2.16; 0.009 difficulty sustaining attention: 1.75 vs 2.47; 0.003 difficulty following directions: 1.75 vs 2.26; 0.002 loses things: 1.15 vs 1.74; 0.002 easily distracted: 1.90 vs 2.84; 0.001 doesn't listen: 1.75 vs 2.26; 0.003 makes careless mistakes: 1.65 vs 2.37; 0.001 difficulty organizing: 1.75 vs 2.42; 0.0065 avoids mental tasks: 1.70 vs 2.42; 0.009 forgetful: 1.80 vs 2.26; 0.004 Impulsivity (DSM-IV) interrupts: 4.00 vs 5.79; <0.001 blurts out: 1.45 vs 2.10; 0.006 difficulty waiting turn: 1.15 vs 1.63; 0.002 acts before thinking: 1.65 vs 2.42; 0.002

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
Bostic 2000 (Fair)	patient report	Adverse event: %pemoline vs %placebo; p-value insomnia: 62% vs 5%; p<0.001 loss of appetite: 38% vs 10%; p=0.014 headache: 29% vs 33%; p=0.763 gastrointestinal pain: 20% vs 10%; p=0.414 agitation: 10% vs 0%; p=0.157 sedation: 0% vs 5%; p=0.317 increased appetite: 5% vs 0%; p=0.317 hearing loss: 5% vs 0%; p=0.317	0	

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

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
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

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
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

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
Ahmann 2001 (Fair)	Weekly completion of (BSEQ) Barkley Side Effects Questionnaire, by parents.	n=79 ethnicity NR ages 10-15y 79.7% males

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
Ahmann 2001 (Fair)	NR	NR/NR/NR	NR/NR/79

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

Author Year (Quality)	Results
Ahmann 2001 (Fair)	**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

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
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)

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**
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

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

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

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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Dextroamphetamine vs. methylphenidate IR				
Arnold 1978 Huestis 1975 Fair	NR	Days 1/2/3+: Dextroamphetamine: 5/10/15 mg Methylphenidate: 10/20/30 mg 3 weeks, then crossover Twice daily: morning and noon	2-week placebo washout	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Dextroamphetamine vs. methylphenidate IR			
Arnold 1978 Huestis 1975 Fair	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	Mean sum CTRS=91.52 CTRS factor I (conduct)=35.83 CTRS factor IV (hyperactivity)=23.10 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

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Dextroamphetamine vs. methylphenidate IR			
Arnold 1978	NR	NR	Mean changes on (p=NS for all):
Huestis 1975	NR	NR	Conners' school behavior checklist by teachers: -21.26 vs -17.97
	29	29	Sum of first 6 items on Davids' Hyperkinetic Rating Scale by teacher: -6.65 vs -5.89
Fair			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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Dextroamphetamine vs. methylphenidate IR				
Arnold 1978 Huestis 1975 Fair	Mean side effects reported by parents on checklist (1=not at all; 4=very much)	p=NS on all Poor appetite: -0.45 vs 0.35 Awake at night: 0.07 vs -0.03 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	NR NR	

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

Study	Study Design Setting	Eligibility criteria
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.

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Efron	NR	Dextroamphetamine 0.15mg/kg	24-hour	NR
1997		Methylphenidate 0.3 mg/kg	washout	
Australia		Both rounded off to the nearest capsule size		
Fair		x 2 weeks then crossover		

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Efron	Wechsler Intelligence Scale for Children, 3rd	8.7 years	ADHD-mixed type=101(81.8%)
1997	Edition (WISC-III), 28-item Conners' Teacher	NR	ADHD-predominantly inattentive=22(17.6%)
Australia	Rating Scale-Revised (CTRS-R), 48-item Conners'	NR	ADHD-predominantly
	Parent Rating Scale-Revised (CPRS-R),		hyperactive/impulsive=2(1.6%)
Fair	Continuous Performance Test (CPT), Child		Mean IQ=98.9
	Behavior Checklist (CBCL)		

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Efron 1997 Australia Fair	NR NR 125	NR NR 125	% 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)

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Efron 1997 Australia Fair	Side Effects Rating Scale (SERS)	Trouble sleeping: 88(70%) vs 79(64%), p=NS Poor appetite: 74(59%) vs 69(56%), p=NS Irritable: 102(82%) vs 100(80%), p=NS Proneness to crying: 95(76% vs 89(71%), p=NS 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)	Total withdrawals nr Withdrawals due to advese events: 2(1.6%) vs 2(1.6%)	

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

Study	Study Design Setting	Eligibility criteria
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.
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Efron 1998 Australia Fair	NR	Dextroamphetamine 0.15mg/kg Methylphenidate 0.3 mg/kg Both rounded off to the nearest capsule size x 2 weeks then crossover	24-hour washout	NR
Elia 1990 United States Fair	Comorbid conduct disorder: 7 (22.6%) Comorbid oppositional disorder: 6 (19.4%) Comorbid specific developmental disorders: 9 (29%)	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	≥ 3 weeks washout	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Efron 1998 Australia Fair	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	ADHD-Mixed type=84(82.4%) ADHD-predominantly inattentive=17(16.7%) ADHD-predominantly hyperactive/impulsive=1(1%) Mean IQ=98.8 Learning disability for reading=30(27.3%) Learning disorder for spelling=36(32.7%)
Elia 1990 United States Fair	CTRS CPRS CGI CPT	Mean age=8.5 years 100% male Race nr	Mean Full Scale WISC-R IQ=102 Mean CTRS factor I (conduct)/factor IV (hyperactivity): 1.3/2.6 Mean CPRS factor I (conduct)/factor IV (hyperactivity): 1.6/2.4 Stimulant naïve: 18 (37.5%)

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Efron 1998 Australia Fair	NR NR 102	NR NR 102	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
Elia 1990 United States Fair	NR NR 31	NR NR NR	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Efron 1998 Australia Fair	SERS	NR	NR NR	
Elia 1990 United States Fair	STESS CPRS	NR	NR NR	

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

Study	Study Design Setting	Eligibility criteria
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).

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Elia 1991 Schmidt 1994 United States Fair	Comorbid conduct disorder: 10 (20.8%) Comorbid oppositional disorder: 12 (25%) Comorbid specific developmental disorders: 11 (22.9%) Comorbid dysthymic disorder: 1 (2%)	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	NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Elia 1991 Schmidt 1994 United States Fair	ABTRS CTRS CPRS CPQ CGI C-GAS CPT Palwin Truncal motor activity monitor	Mean age=8.6 years 100% male	Mean Full Scale WISC-R IQ=105.6 Mean CTRS factor I (conduct) - teacher/parent rating: 1.3/1.5 Mean CTRS factor IV (hyperactivity) - teacher/parent rating: 2.6/2.4 Stimulant naïve: 18 (37.5%)

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Elia 1991 Schmidt 1994 United States Fair	NR NR 48	NR NR NR	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Elia 1991 Schmidt 1994 United States Fair	STESS CPRS	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	NR NR	

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

Study	Study Design Setting	Eligibility criteria
Casellanos 1997 United States	RCT with crossover Single center	(1) DSM-III-R criteria for Tourette's disorder with tics confirmed by a knowledgeable clinician at least 1 year prior to referral (Tourette Syndrome Classification Study Group, 1993); (2) symptoms of ADHD present in at least two settings; (3) Conners hyperactivity factor scores from their home teacher were at least 2 SD greater than age norms
Subgroup of Elia 1991		Tourette's syndrome

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Casellanos 1997 United States Subgroup of Elia 1991	Conduct disorder=1(5%) Oppositional defiant disorder=6(30%) Reading disorder=1(5%) Overanxious disorder=1(5%) Obsessive-compulsive disorder=2(10%) Enuresis=4(20%)	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.	≥ 4 weeks washout	Haloperidol

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Casellanos 1997 United States Subgroup of Elia 1991	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	WISC-R Full Scale IQ=98.8 WISC-R Verbal=102 WISC-R Performance=95.6 Yale Global Tic Severity Scale (0-104)=37.3 CTRS Conduct/Hyperactivity factors=0.59/1.98 C-GAS=42.6

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Casellanos 1997 United States Subgroup of Elia 1991	NR NR Enrolled: Group 1=22, Group 2=6, Group 3=4	# withdrawn: Group 1=2(9.1%), Group 2=nr, Group 3=n4/lost to fu nr/Analyzed: Group 1=20, Group 2=nr, Group 3=nr	Tic severity Dextroamphetamine had greater severity than placebo (+25%), p<0.05 Methylphenidate severity indistinguishable from placebo (-4%), p=NS

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Casellanos	NR	# cases with dextroamphetamine vs methylphenidate (denominate	NR	
1997		unclear)	NR	
United States		Marked appetite suppression with transient weight loss: 4 vs 3 Initial insomnia: 10 vs 2		
Subgroup of Elia 1991		Transient obsessive-compulsive symptoms: 1 vs 5		

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

Study	Study Design Setting	Eligibility criteria
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.
Kauffman 1981 Fair	RCT with crossover Single center	Children diagnosed as "hyperactive," according to a set of predetermined clinical criteria

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Elia 1993 United States Fair	Comorbid conduct disorder: 6 (18.2%) Comorbid oppositional disorder: 7 (21.2%) Comorbid developmental disorders: 9 (27.3%)	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.	≥ 3 weeks washout	NR
Kauffman 1981 Fair	NR	Dextroamphetamine 10-60 mg Methylphenidate 5-30 mg Placebo Twice daily: morning and noon 6 weeks, then crossover	NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Elia 1993 United States Fair	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	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
Kauffman 1981 Fair	Urine sample Returned capsules were recorded	Mean age nr 100% male 100% white	NR

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Elia	NR	NR/NR/33	Combined Reading Scores
1993	NR		*Percent correct*
United States	33		Dextroamphetamine vs placebo=89.5 vs 86.1; p<0.01 Methylphenidate vs placebo=89.7 vs 86.1; p<0.01
Fair			
			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
Kauffman	NR	NR/NR/12	% patients with positive urinalysis: 60 vs 67; p=NS
1981	NR		% of patient-weeks with missed doses recorded: 18 vs 13; p=NS
	12		
Fair			

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Elia 1993 United States Fair	STESS	% 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	Withdrawals due to adverse events: 0 vs 0	
Kauffman 1981 Fair	Side effects checklist (not specified)	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	NR NR	

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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Gross 1976 Poor	NR	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	None	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Gross 1976 Poor	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	NR

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Gross 1976 Poor	NR NR 50	2 (4%) withdrawn/lost to fu nr/analyzed: dextroamphetamine=48 vs methylphenidate=46	Average improvement: 2.3 vs 2.2; p=NS

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Gross 1976 Poor	Use of same 8-point scale used for efficacy (-2=much worse to +5=outstanding improvement)	Average improvement in average side effects: 0.4 vs 0.5; p=NS	2 (4%) NR	

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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Borcherding 1990 Poor	NR	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.	3-week washout	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Borcherding 1990 Poor	Efficacy nr	Mean age=8.6 years 100% male 71.7% white, 2.2% black, 6.5% hispanic/asiatic	WISC-R Full Scale IQ=106.1 Mean CTRS for Factor 4 (hyperactivity)/Factor 1 (conduct): 2.5/1.2 28.3% stimulant naïve

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Borcherding	NR	1 (2.2%)	Efficacy nr
1990	NR	withdrawn/lost to fu	
	46	nr/# analyzed ranged	
Poor		by outcome	

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Borcherding 1990 Poor	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)	<u>Abnormal movements</u> 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%) <u>Compulsive behaviors</u> 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 <u>STESS items (mean scores)</u> 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 <u>CPRS items (mean scores) (all "both > placebo)</u> Compulaive acts: 1.7 vs 1.5 Nervous habits & mannerisms: 1.8 vs 1.7 Obsessive thinking: 2.0 vs 2.0	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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Sharp 1999 Fair	NR	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	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)

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Sharp 1999 Fair	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	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

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Sharp 1999 Fair	150/NR/32	1 (3.1%) withdrawn/lost to fu nr/analyzed=32	% patients with CGI--GI ratings of "very much improved" or "much improved": 85% vs 83%; p=NS

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Sharp 1999 Fair	NR	Mean change in body weight (kg) Dextroamphetamine: -1.1; p=0.01 from baseline Methylphenidate: -0.4; p=NS from baseline	1 (3.1%) total withdrawals Withdrawals due to adverse events nr	Meta-analysis of this 100% female trial

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

Study	Study Design Setting	Eligibility criteria
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.

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Simpson 1980 United States Fair	NR	MPH, D-amphetamine, placebo for 8 weeks each	NR/NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Simpson 1980 United States Fair	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	NR

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Simpson 1980 United States Fair	NR/NR/12	NR/NR/12	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.

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Simpson 1980 United States Fair	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.	NR	0 withdrawals; 0 withdrawals due to adverse events	

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

Study	Study Design Setting	Eligibility criteria
Adderall versus methylphenidate		
Barkley 2000 Poor	RCT with crossover Single center	DSM-IV criteria for ADHD

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Adderall versus methylphenidate				
Barkley 2000 Poor	NR	Adderall 10 mg and 20 mg Methylphenidate 10 mg and 20 mg Placebo 1 week, then crossover Twice daily: morning and noon	NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Adderall versus methylphenidate			
Barkley 2000 Poor	ADHD/ODD Rating Scale, Conners CPT, Stroop Word-Color Association Test, CGI	n=35 Mean age=14 85.7% male Race nr	Mean IQ=103.9

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Adderall versus methylphenidate			
Barkley 2000 Poor	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	Mean scores for Adderall 5 mg/10 mg vs methylphenidate 5 mg/10 mg vs placebo: <u>Parent ratings</u> 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 <u>Teen self-ratings</u> ODD Total: 6.0/5.8 vs 5.6/5.2 vs 5.1 <u>English Teacher</u> 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 <u>Math Teacher</u> 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 <u>In-clinic tests</u> 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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Adderall versus methylphenidate				
Barkley 2000	SERS	Mean scores for Adderall 5 mg/10 mg vs methylphenidate 5 mg/10 mg vs placebo:	NR NR	
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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Pelham 1999a Fair	NR	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	First 2 weeks of the program served as a period of baseline observation (unclear if run-in/washout used)	Concurrent behavioral point system

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Pelham 1999a Fair	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	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

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Pelham 1999a Fair	NR/NR/21	NR/NR/NR	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 1999a Fair	Frequency with which raters endorsed any side effect as either moderate or severe on at least 1 day	% 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	NR NR	

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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Pelham 1999b Fair	NR	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	First 2 weeks of the program served as a period of baseline observation (unclear if run-in/washout used)	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Pelham 1999b Fair	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	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

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Pelham 1999b Fair	NR/NR/25	NR/NR/NR	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 1999b Fair	Frequency with which raters endorsed any side effect as either moderate or severe on at least 1 day	% 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	1 (4%) withdrawal due to exacerbation of pre-existing motor tics	

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

Study	Study Design Setting	Eligibility criteria
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	See Pelham 1999a

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Chronis 2003 (same as Pelham 1999a)	Parent affect: Positive and Negative Affect Schedule (PANAS) - comprised of two 10-item subscales (PA=positive affect, NA=negative affect)	See Pelham 1999a	See Pelham 1999a
Fair	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)		

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Chronis 2003 (same as Pelham 1999a) Fair	See Pelham 1999a	See Pelham 1999a	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**

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
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

Study	Study Design Setting	Eligibility criteria
Pliszka 2000	RCT	DISC criteria for ADHD; ≥ 1.5 SD above the mean for his/her age and sex on the IOWA
Faraone 2001	Parallel	CTRS Inattention/Overactivity (I/O) factor; parent Conners Global Index score similarly elevated
Fair		

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Pliszka 2000	NR	Adderall	NR/NR	NR
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		

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Pliszka 2000 Faraone 2001 Fair	IOWA CTRS, Conners Global Index, CGI	Mean age=8.2 Gender nr Race nr	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

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Pliszka 2000 Faraone 2001 Fair	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	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Pliszka 2000 Faraone 2001 Fair	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"	All p=NS Facial tics: 1 (5%) vs 0 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%)	Total withdrawals=5 (8.6%) Withdrawals due to adverse events: 2 (10%) vs 1 (5%), p=NS	

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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Manos 1999 Poor	Oppositional defiant disorder=21.4%	Adderall (once daily) vs methylphenidate (twice daily) 1-week for each condition 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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Manos 1999 Poor	ARS, Conners ASQ, SSQ-R	Mean age=10.1 78.6% male 92.8% white	Inattentive type=45.2% Combined type=54.8% Mood disorder=1.2% Anxiety disorder=4.8% Learning disability=47.6%

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Manos 1999 Poor	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	"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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Manos	SE/BMS	Results described as "no differences", but p-values nr	NR	
1999		Insomnia: 5 (11.9%) vs 2 (4.8%)	NR	
		Decreased appetite: 0 vs 1(2.4%)		
Poor		Tics/nervousness: 0 vs 0		

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

Study	Study Design Setting	Eligibility criteria
IR versus SR formulations of methylphenidate		
Bergman 1991 United States Poor	CCT Crossover Setting NR	DSM-III diagnosis of Attention Deficit Disorder with Hyperactivity (ADDH)

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
IR versus SR formulations of methylphenidate				
Bergman 1991 United States Poor	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)	Sustained-release methylphenidate 20 mg (single morning dose) Short-acting (regular) methylphenidate 10 mg (twice daily - morning and afternoon) Placebo 1 day	NR/NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
IR versus SR formulations of methylphenidate			
Bergman 1991 United States Poor	Identical Pairs version of the CPT (CPT-IP)	Mean age nr (between 6 and 12) 100% male Ethnicity nr	NR

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
IR versus SR formulations of methylphenidate			
Bergman 1991 United States Poor	NR/NR/42	NR/NR/NR	SR methylphenidate = short-acting methylphenidate on all measures (data nr)

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
IR versus SR formulations of methylphenidate				
Bergman 1991 United States Poor	NR	NR	NR NR	

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

Study	Study Design Setting	Eligibility criteria
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)

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Fitzpatrick 1992 Poor quality	63.1% oppositional disorder	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	NR/NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Fitzpatrick 1992 Poor quality	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	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

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Fitzpatrick 1992 Poor quality	NR/NR/19	NR/NR/NR	SR vs SA vs Combination (SR+SA) p=NS for all All outcomes reported for Parent/Teacher 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 Other ratings: 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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Fitzpatrick 1992 Poor quality	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	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	NR NR	

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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Pelham 1987 Poor	4 (30.8%) with Conduct Disorder 6 (46.1%) with Oppositional Defiant Disorder 3 (23.1%) with Learning Disability	Placebo (twice daily) Methylphenidate 20 mg (twice daily) Sustained release methylphenidate 20 mg (once daily) Condition varied daily and 5 to 9 days of data were gathered per medication condition	NR/NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Pelham 1987 Poor	Daily Frequencies=frequencies with which numberous appropriate and inappropriate behaviors occurred daily Time out=average number of time outs per day Classroom measures=rates of on-task beahvior 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	WISC-R IQ=95.3 ACRS Parent/Teacher=17.7/19.0 IOWA CTRS 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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Pelham 1987 Poor	NR/NR/13	NR/NR/NR	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Pelham	NR	Evidence of anorexia: Standard methylphenidate=4 (30.8%) vs 5	NR	
1987		(38.5%); p=NS	NR	
Poor				

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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Pelham 2001 Fair	Oppositional defiant disorder=43% Conduct disorder=37%	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	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

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Pelham 2001 Fair	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) nonc	Mean age 9.1 89% male 94% white	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

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Pelham 2001 Fair	NR/NR/70	2 (2.8%) withdrawn/lost to fu nr/analyzed 68 5 children missed one of 3 testing sessions	Placebo / tid IR MPH / Concerta, p-value = MPH IR vs Concerta <u>Natural setting</u> 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) <u>Recreational Activities --</u> 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 <u>Recess measures (means)</u> 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 <u>Laboratory sessions (means) (overall daily measures)</u> 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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 2001 Fair	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	Placebo vs qd Concerta vs tid IR MPH Serious adverse events: 0 vs 0 vs 0 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%)	2 (2.8%) withdrawals overall (group assignment unclear) Withdrawals due to adverse events: none reported	

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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Cox 2004 Fair	NR	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	24 hour washout	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Cox 2004 Fair	Atari Research Driving Simulator Composite Score (Imparied Driving Score) consisting of Off Road, Veering Across Midline, Standard Deviation Steering, Inappropriate Braking, % Missed Stop Sgianls, % Bumps, and % Crashes	Mean age =17.2 100% male Race NR	Inattentive type=4(66.7%) Combined type=2(33.3%) Proportion taking medicatin for ADHD at baseline NR Mean baseline dose of MPH NR

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Cox 2004 Fair	NR/NR/7	1 (14.3%) withdrawn/0 lost to fu/analyzed=6	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Cox 2004 Fair	NR	NR	1 (14.3%) withdrawals 0 due to adverse events	

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

Study	Study Design Setting	Eligibility criteria
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)

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Wolraich 2001 United States Fair	46.5% ODD 11.3% Conduct Disorder 5.3% Tic Disorder 1.4% Anxiety Disorder 0.7% Depression	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	NR/NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Wolraich 2001 United States Fair	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	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

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Wolraich 2001 United States Fair	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)	Mean change in IOWA Conners Scores (OROS MPH vs IR MPH) (p-values NR, but narrative states there are NS differences): Teacher/Parent scores: Inattention/Overactivity: -3.76/-4.79 vs -3.59/-3.73 Oppositional/Defiance: -1.6/-3.24 vs -1.3/-2.36 Mean changes in secondary measures of efficacy (teacher ratings) 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 Mean change in secondary measures of efficacy (parent ratings) 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 Investigator ratings 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% Other 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%

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Wolraich 2001 United States Fair	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	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	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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Whitehouse 1980 United States Fair	NR	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	Run-in: one month of standard methylphenidate 20 mg (twice daily) prior to study/no washout	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Whitehouse 1980 United States Fair	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	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)

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Whitehouse 1980 United States Fair	NR/NR/34	4 (11.8%) withdrawn/0 lost to fu/30 analyzed	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Whitehouse 1980 United States Fair	NR	Adverse reactions: 5 (31.3%) vs 2 (14.3%), p=NS (consisted of headache, hyperactivity and restlessness)	4 (11.8%) (group assignment NR) No withdrawals due to adverse events	

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

Study	Study Design Setting	Eligibility criteria
Clonidine versus Methylphenidate		
Tourette's Syndrome Study Group 2002 Fair	RCT Parallel Multicenter	Subjects aged 7-14 years, in school, and of any race or ethnic background; DSM-IV criteria for ADHD; teacher ratings of ADHD symptoms above specified cutoff scores on the IOWA CTRS (boys: grade 2-3=10, grade 4 and above=9; girls: grade 2-3=7, grade 4 and above=6); DSM-IV criteria for Tourette disorder

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Clonidine versus Methylphenidate				
Tourette's Syndrome Study Group 2002 Fair	Tourette's syndrome Other psychiatric diagnoses OCD: 15.8% ODD: 38.1% Conduct disorder: 9% GAD: 9.2% MDD: 5%	Mean doses: Clonidine 0.25 mg Methylphenidate 25.7 mg Combination (clonidine+methylphenidate) 0.28 mg and 26.1 mg Placebo Flexible dosing, initiated at once daily and increased to 2-3 time daily within a few days 4-week titration period, followed by 8 weeks of maintenance therapy,	NR/NR	Nonpharmacologic (e.g., behavioral) interventions were allowed, but remained unchanged throughout the course of the study

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Clonidine versus Methylphenidate			
Tourette's Syndrome Study Group 2002 Fair	ASQ-Teacher, Iowa CTRS, ASQ-Parent, Conners CPT; systematic classroom observations of the subject's behavior; Yale Global Tic Severity Scale (YGTSS); Tic Symptom Self Report Scale (TSSR); Global Tic Rating Scale (GTRS); Child-Yale Brown Obsessive Compulsive Scale (C-YBOCS); Children's Global Assessment Scale (C-GAS)	Mean age=10.2 85.4% male 88.3% white	Tic Disorder Diagnosis Tourette syndrome: 94% Chronic motor tic disorder: 5% Chronic vocal tic disorder: 1% ADHD subtype Inattentive: 71.3% Hyperactive/impulsive: 2.3% Combined: 26.4% Mean rating scale scores ASQ-Teacher: 14.6 ASQ-Parent: 18.1 IOWA CTRS I/O, O/D, Total: 9.1, 3.8, 12.9 YGTSS Motor, Verbal, Total: 11.3, 9.0, 40.6 GTRS Teacher, Parent: 8.6, 11.0 Classroom observations On-task behavior: 76.7% Disruptive behavior: 10.9%

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Clonidine versus Methylphenidate			
Tourette's Syndrome Study Group 2002 Fair	NR/148/136	19 (14%) withdrawn/0 lost to fu/136 analyzed	Treatment effects for clonidine vs placebo; methylphenidate vs placebo; combination therapy vs placebo (all p-values are vs placebo): ASQ-Teacher: 3.3, p=0.02; 3.3, p=0.02; 6.3, p<0.0001 ASQ-Parent: 4.7, p=0.009; 5.5, p=0.002, 5.9, p=0.002 Iowa Conners Total: 2.4, p=NS, 3.0, p=0.04; 4.8, p=0.0009 I/O: 1.7, p=0.05; 1.8, p=0.04; 3.5, p<0.0001 O/D: 0.7, p=NS; 1.2, p=NS; 1.3, p=0.05 Classroom observation On task: 4.1, p=NS; 10.2, p=0.02; 11.2, p=0.02 Disruptive: 2.3, p=NS; 1.0, p=NS; 5.1, p=NS Conners CPT Commissions: 0.8, p=NS; 2.6, p=NS; 3.2, p=NS Hit Rxn. Time: -3.8, p=NS; -4.5, p=NS; -4.4, p=NS Attentiveness: 0, p=NS; 7.0, p=NS; 9.3; p=0.02 Risk Taking: 4.8, p=NS; 9.1, p=NS; 20.6; p=0.0005 YGTSS Motor: 2.1, p=0.05; 1.3, p=NS; 2.3, p=0.03 Vocal: 2.4, p=0.05; 1.3, p=NS; 2.3, p=0.03 OI: 6.3, p=0.007; 5.8, p=0.01; 6.0, p=0.01 Total: 10.9, p=0.003; 9.4, p=0.01; 11.0, p-0.003 GTRS-parent: 3.2, p=0.02; 3.1, p=0.03; 3.5, p=0.01 GTRS-teacher: 2.1, p=NS; 1.5; p=NS; 3.2, p=0.009 TSSR-Parent Motor: 3.9, p=0.03; 3.8, p=0.04; 4.7, p=0.01 Vocal: 1.4, p=NS; 1.4, p=NS; 0.8, p=NS C-GAS: 9.0, p=0.003, 9.8, p=0.001; 14.5, p<0.0001

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Clonidine versus Methylphenidate				
Tourette's Syndrome Study Group 2002 Fair	NR	Clonidine vs methylphenidate Sedation (% patients): 48% vs 14%; p=0.004 Sedation (% patients rated as moderate or severe): 35% vs 8%; p=0.007	<u>Total Withdrawals</u> MPH=4(10.8%) Clonidine=4 (11.8%) Combination=4 (12.1%) Placebo=7 (21.9%) <u>Withdrawals due to adverse events</u> Combination=1 (3.4%) for ECG change; no other withdrawals due to adverse events in other groups	

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

Study	Study Design Setting	Eligibility criteria
van der Meere 1999 The Netherlands Fair	RCT Parallel Setting NR	Children, age range 7 to 12 years, all diagnosed with ADHD (DSM-III-R)
Connor 2000 US	RCT, DB, parallel, pilot study. 3 subjects refused randomization to the MPH alone study arm and so were partially randomized to the	Children aged 6-16 years meeting DSM-III-R criteria for ADHD and either Aggressive Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD) and to have a score of 1.5 standard deviations above the mean for age and gender on the Parent Child Behavior Checklist (CBCL) Attention Problems Scale and a score on the Teacher Child Attention Problem Rating Scale (CAPS) of at least the 93rd percentile.

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
van der Meere 1999 The Netherlands Fair	6 (11.3%) Conduct Disorder 14 (26.4%) Oppositional Defiant Disorder 2 (3.8%) Depressive/Anxiety Disorder	Methylphenidate 0.6 mg/kg Clonidine 4.0 μg/kg (using 25 μg Dixarit dragees) 7 weeks Twice daily dosing: Methylphenidate=breakfast/lunch; Clonidine=breakfast/evening	NR/NR	NR
Connor 2000 US	ODD or CD	Clonidine maximum, flexibly titrated based on clinical efficacy and reported side effects, of 0.3 mg three times daily (mean dose 0.17 mg/d) vs Methylphenidate (MPH) maximum, flexibly titrated based on clinical efficacy and reported side effects, of 40 mg twice daily (mean dose 32.5 mg/d)	48 hour open drug washout before screening	All were free of medication at baseline.

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
van der Meere 1999 The Netherlands Fair	Response inhibition task (press a response button when a "P" appeared on a monitor display; disregaring presentations of "R" and stars; a low, medium and high speeds	Mean age=9.2 86.8% male Ethinicity NR	Mean Full Scale IQ=90
Connor 2000 US	Disruptive Behavior Scale (DBS) at baseline, 1 month, 2 months, 3 months. Academic Performance Rating Scale (APRS) at baseline, 1 month, 2 months, 3 months. Home Situations Questionnaire (HSQ) at baseline, 1 month, 2 months, 3 months. School Situations Questionnaire (SSQ) at baseline, 1 month, 2 months, 3 months.	Mean age 9.1 years Gender NR 23 (96%) White 1 (4%) African American	11 (46%) had history of receiving MPH prior to study. No child has a previous treatment history with any other psychiatric medication.

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
van der Meere 1999 The Netherlands Fair	NR/NR/53	NR/NR/53	Two-way MANOVA (groups, session) Mean RT: F(2, 50) - 1.83, p<0.17 Errors: F(2, 50 = 0.69, p<0.51 Contrast MANOVA analysis for each condition separately for RT MPH vs Clonidine: F(1,33) = 4.6, p<0.05 Variability of responding: F(2, 50) = 2.02, p<0.15
Connor 2000 US	NR/NR/24	0/0/24	Clonidine only (n=8) vs Methylphenidate (MPH) only (n=8) [MPH and clonidine combined (n=8) results are not included here] <u>Parent Ratings</u> No interaction was found to be significant for group X time. <u>Teachers Ratings</u> SSQ Number of Problem Settings

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
van der Meere 1999 The Netherlands Fair	NR	NR	NR NR	
Connor 2000 US	Number and severity of side effects were reported by parents and teachers. Pulse, systolic and diastolic blood pressure, EKG data, height, and weight were analyzed.	No differences over time were found for number of parent-reported side effects. Parents reported a decreasing mean of severity of side effects with time across all 3 groups.		

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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Extended release formulations of Methylphenidate				
Lopez 2003 Fair	NR	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)	NR/NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Extended release formulations of Methylphenidate			
Lopez 2003 Fair	(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	NR

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Extended release formulations of Methylphenidate			
Lopez 2003 Fair	NR/NR/36	0 withdrawn/0 lost to fu/36 analyzed	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Extended release formulations of Methylphenidate				
Lopez 2003 Fair	NR	Number (proportion) patients with at least one adverse event: 1 (2.7%) vs 1 (2.7%) vs 1 (2.7%)	Total withdrawals=0 Withdrawals due to adverse events=0	

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

Study	Study Design Setting	Eligibility criteria
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.

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Other comparisons to methylphenidate				
Conners, 1980	NR	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.	None/8 day washout for hyperkinesis medications and 6 months for phenothiazines	None

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Other comparisons to methylphenidate			
Conners, 1980	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%)	NR

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Other comparisons to methylphenidate			
Conners, 1980	88/NR/60	NR/NR/60	**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 v *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)

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Other comparisons to methylphenidate				
Conners, 1980	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.	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.	NR	

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

Study	Study Design Setting	Eligibility criteria
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)

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Kratochvil 2002 United States/Canada Fair	Oppositional/defiant disorder = 52.6% Major depressive disorder = 6.6% Elimination disorder = 16.7%	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	NR/NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Kratochvil	Primary measure: Investigator-rated ADHD RS	Mean age=10.4	ADHD subtype
2002	Secondary measures: Parent-rated version of the	92.5% male	Combined: 75.9%
United States/Canada	ADHD RS; Conners Parent Rating Scale-Revised:	76.7% white	Hyperactive-impulsive: 1.3%
	Short Form (CPRS-R); Clinical Global Impression-		Inattentive: 22.8%
Fair	ADHD-Severity scale		ADHD RS-Parent scored (mean): 76.7

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Kratochvil	319/NR/228	85 (37.3%)	Atomoxetine vs methylphenidate (mean changes) (p=NS for all)
2002		withdrawn/5 (2.2%)	ADHD RS Total score: -19.44 vs -17.78
United States/Canada		lost to fu/218 analyzed	ADHD RS Hyperactivity/Impulsivity: -9.50 vs -8.48
		(atomoxetine n=178;	ADHD RS Inattention subscale: -9.94 vs -9.30
Fair		methylphenidate n=40)	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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Kratochvil 2002 United States/Canada Fair	Administration of open-ended questions and collection of ECG and laboratory data	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	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

Study	Study Design Setting	Eligibility criteria
Buitelaar 1996 The Netherlands Fair	RCT Crossover Utrecht Department of Child Psychiatry	(1) Diagnosis of ADHD according to DSM-III-R criteria; (2) scores in the clinical range on both the CBCL and CTRS hyperactivity factors; (3) deficits in attention performance on either a reaction-time task or a continuous performance task in the neuropsychological testing; (4) no previous treatment with psychotropic medication; and (5) a clinical indication for drug treatment
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Buitelaar 1996 The Netherlands Fair	Conduct disorder = 20 (38.5%) Depressive disorder = 8 (15%) Anxiety disorder = 22 (42%)	Pindolol: single dose of 20 mg for 3 days, then 40 mg (administered twice daily at breakfast and noon) Methylphenidate: single dose of 10 mg for 3 days, then 20 mg (administered twice daily at breakfast and noon) Fixed dosing 4 weeks; drug-free interval of 2 weeks; then crossover	NR/NR	NR/NR
Stephens 1984 United States Poor quality	NR	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	NR/NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Buitelaar 1996 The Netherlands Fair	Hyperactivity, conduct and anxiety factor sum scores from the 93-item Conners' Parent Rating Scale (CPRS) x weeks 0, 2 and 4 10-item Abbreviated Conners rating Scale (ACRS) 39-item Conners Teachers' Rating Scale (CTRS)	Mean age=9.1 93.7% male Race nr	WISC-R IQ=93.2 CBCL Inattentiveness/hyperactivity=74.4 Externalizing symptoms=61.9 Internalizing symptoms=68.5 Conners' Parents' Rating Scale Abbreviated scale=3.0 Hyperactivity=2.6 Conduct=1.9 Conners' Teachers' Rating Scale Abbreviated scale=2.4 Hyperactivity=2.7 Conduct=1.4
Stephens 1984 United States Poor quality	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	ACRS mean score=17.9

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Buitelaar 1996 The Netherlands Fair	NR/NR/32 (see comments)	0 withdrawn/0 lost to fu/32 analyzed (pindolol n=11, methylphenidate n=10, placebo n=11)	Pindolol vs methylphenidate Results at weeks 2/4 (mean change) ACRS estimated from Figure ACRS at clinic: nr/-0.3 vs nr/-0.05, p<0.05 ACRS at school: -0.1/-0.2 vs -0.4/-0.45; p=NS ACRS at home: -0.1/-0.2 vs -0.1/-0.2; p=NS Conners' Teacher Rating Scale Hyperactivity: -0.1/-0.3 vs 0/0, p=NS Conduct: 0/0 vs -0.3/-0.2, p=NS Anxiety: 0/-0.1 vs 0/0, p=NS Conners' Parent Rating Scale Hyperactivity: -0.1/-0.2 vs -0.2/-0.3, p=NS Conduct: -0.1/-0.2 vs -0.1/-0.1, p=NS Anxiety: 0/0 vs 0/-0.1, p=NS Clinical ratings CGI severity: nr/-0.4 vs nr/-0.5, p=NS
Stephens 1984 United States Poor quality	NR/NR/31	NR/NR/NR	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Buitelaar 1996 The Netherlands Fair	Adverse effects were rated by the parents after 2 and 4 weeks of treatment on a checklist encompassing 20 possible side-effects of methyphenidate and beta-blockers. This checlist was modified from the Stimulant Drug Side Effects Rating Scale (Barkley, 1990)	Chi-square (df=2) was ns for all but paresthesias Insomnia: 5 (46%) vs 4 (38%) vs 3 (25%) Anorexia: 2 (15%) vs 2 (24%) vs 3 (25%) Incoherent speech: 3 (25%) vs 2 (15%) vs 2 (18%) Stomach pain: 2 (20%) vs 1 (12%) vs 3 (25%) Nausea: 1 (10%) vs 2 (16%) vs 2 (17%) Tiredness: 3 (25%) vs 2 (18%) vs 1 (8%) Headache: 2 (20%) vs 2 (20%) vs 3 (25%) Sedation: 1 (13%) vs 1 (8%) vs 1 (8%) Anxiety: 3 (25%) vs 2 (16%) vs 2 (16%) Irritability: 1 (10%) vs 3 (29%) vs 3 (27%) Moodiness, dysphoria: 2 (16%) vs 3 (33%) vs 3 (27%) Tics: 1 (8%) vs 1 (10%) vs 0 (0%) Social Isolation: 1 (5%) vs 1 (8%) vs 0 (0%) Nightmares: 1 (10%) vs 1 (8%) vs 1 (8%) Hallucinations: 1 (10%) vs 1 (4%) vs 0 (0%) Paresthesias: 1 (10%) vs 0 vs 0; p<0.05	NR NR	Pindolol dropped from the study design after first 32 subjects were enrolled due to association with troublesome, and intense adverse effects (e.g., vivid visual hallucinations and nightmares); last 20 subjects randomized to methylphenidate
Stephens 1984 United States Poor quality	NR	NR	NR NR	

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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Barrickman 1995 United States Fair quality	Conduct disorder = 2 (13.3%) Oppositional defiant disorder = 2 (13.3%) Developmental learning disorders = 5 (33.3%)	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	No run-in/Washout of 14 days	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Barrickman 1995 United States Fair quality	Iowa Conners Abbreviated Parent and Teacher Questionnaire (ICQ); physician-rated Clinical Global Impression (CGI)	Mean age of 11.8 80% male 100% Caucasian	Treatment-naïve=5 (33.3%) WISC-R Full Scale IQ score=106 WISC-R Verbal score=104 WISC-R Performance score=108

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Barrickman 1995 United States Fair quality	NR/NR/18	3 (16.7%) withdrawn/0 lost to fu/15 analyzed	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Barrickman 1995 United States Fair quality	NR	Bupropion vs MPH % patients with any adverse event: 9 (60%) vs 5 (33.3%); p=NS Drowsiness: 4 (26.7%) vs 1 (6.7%) Fatigue: 3 (20%) vs nr 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%)	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

Study	Study Design Setting	Eligibility criteria
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

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Multiple Comparisons				
James 2001 United States Poor	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%)	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.	Run-in NR/3-week washout	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Multiple Comparisons			
James 2001 United States Poor	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	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

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Multiple Comparisons			
James 2001 United States Poor	NR/38 enrolled/35 randomized	0/0/35	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Multiple Comparisons				
James 2001 United States	Stimulant Side Effect Rating Scale: rated by nurse coordinator	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	0 withdrawals; 0 withdrawals due to adverse events	
Poor	Barkley Side Effect Rating Scale: rated by parents	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		

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

Study	Study Design Setting	Eligibility criteria
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)

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

Study	Comorbidity	Interventions and total daily dose Duration Dosing schedule	Run-in/Washout Period	Allowed other medications/ interventions
Pelham 1990 Poor	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%)	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	NR/NR	NR

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

Study	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics (mean scores)
Pelham 1990 Poor	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	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

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

Study	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed	Results
Pelham 1990 Poor	NR/NR/22	NR/NR/NR	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

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

Study	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Pelham 1990 Poor	NR	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	NR NR	

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 1997	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
Casellanos 1997	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Efron 1998	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 1997	NR	Yes	No	Fair	NR NR 125	NR	24-hour 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
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
Efron 1998	NR	Yes	No	Fair	NR NR 102	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
Efron 1997	NO	Yes	NR	Yes
Elia 1991	No	Yes	NR	Yes
Elia 1993	No	Yes	NR	No
Casellanos 1997	No	Yes	NR	No
Efron 1998	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
Elia 1990	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Arnold 1978 Huestis 1975	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Gross 1976	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Borcherding 1990	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**
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
Arnold 1978 Huestis 1975	NR	Yes	No	Fair	NR NR 29	NR	2-week placebo washout
Gross 1976	NR	No	Unclear	Poor	NR/NR/50	NR	No/No
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

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
Elia 1990	NO	Yes	NR	Yes
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
Gross 1976	NR	Yes	NR	Unclear
Borcherding 1990	28.30%	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
Sharp 1999	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Kauffman 1981	NR	Yes	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
Pelham 1999a	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**
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
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
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
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

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
Kauffman 1981	NR	Yes	Ciba-Geigy Corp.	Yes
Barkley 2000	NR	Yes	Shire	Yes
Pelham 1999a	24%	Yes	Shire	No; Summer Treatment Program with behavioral training for both children and parents

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 1999b	NR	NR	Crossover	Yes	Yes	Yes	Yes	NR NR NR NR
Pliszka 2000 Faraone 2001	NR	NR	Yes	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

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 1999b	NR	Yes	No	Fair	NR/NR/25	NR	NR/NR
Pliszka 2000 Faraone 2001	No	Yes	No	Fair	73 screened/eligible unclear/enrolled 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
Manos 1999	NR	Yes	No	Poor	Referred=60/eligible =NR/participated=159	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
Pelham 1999b	NR	Yes	Shire	No; Summer Treatment Program with behavioral training for both children and parents
Pliszka 2000 Faraone 2001	46 (79.3%)	Yes	Shire	Yes
Manos 1999	NR	Yes	NIDA, Maternal and Child Health Program	No

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
Bergman 1991	Inadequate (counterbalanced order)	NR	n/a - crossover	No	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
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
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

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**
Bergman 1991	NR	Unclear	Unclear	Poor	NR/NR/42	NR	NR/NR
Fitzpatrick 1992	NR	Unclear	Unclear	Poor	NR/NR/19	NR	NR
Pelham 1987	NR	Unclear	Unclear	Poor	NR/NR/13	NR	NR
Pelham 1990	NR	Unclear	Unclear	Poor	NR/NR/22	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

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
Bergman 1991	NR	Yes	NIMH Grants (MH 38838-05 and MH 30906-09)	Unclear
Fitzpatrick 1992	94.7% naïve to psychotropic medication	Yes	NIMH Grant MH38118, CIBA-GEIGY provided placebo tablets	No
Pelham 1987	NR	Yes	NR	No, Summer Treatment Program
Pelham 1990	NR	Yes	NR	No, Summer Treatment Program+behavior modification intervention
Cox 2004	No	Yes	McNeil Consumer and Specialty Pharmaceuticals	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
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**
Wolraich 2001	No/No	Yes	No	Fair	Screened=500/Enrolled=405/Randomized=312	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
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
Wolraich 2001	No	Yes	Alza	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
Lopez 2003	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	Yes NR NR NR
Kratochvil 2002	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR
Buitelaar 1996	NR	NR	n/a - crossover	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**
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
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
Buitelaar 1996	NR/NR	Yes	No	Fair	NR/NR/32	Diagnosis of tic disorder or pervasive developmental disorder, a family history of tic disorder, and the usual contra-indications for treatment with beta-blockers such as cardiac diseases, in particular conduction abnormalities and bradycardia, hypotension, obstructive pulmonary diseases and insulin-dependent diabetes	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
Kratochvil 2002	No	Yes	Eli Lilly	Yes
Buitelaar 1996	Yes	Yes	NR	No - class naïve patients only

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
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
Barrickman 1995	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	Yes NR NR NR
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

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**
Stephens 1984	NR/NR	Unclear	Unclear	Poor	NR/NR/36	NR	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
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

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
Stephens 1984	Unclear for 25 (69.4%); reported that 11 were taking stimulants at time of study	Yes	NR	Unclear
Barrickman 1995	No	Yes	NR	Yes
James 2001	42.8% class naïve	Yes	NR	No, research school setting

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
Pelham 2001	NR	NR	n/a - crossover	Yes	Yes	Yes	Yes	Yes, NR, Yes (virtually 100%), NR
Simpson 1980	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**
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
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
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

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
Pelham 2001	No	Yes	Alza	Yes
Simpson 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
Connor 2000	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes NR NR NR
Conners 1980	NR	NR	No	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**
Connor 2000	No	Yes	No	Fair	NR/NR/24	NR	NR
Conners 1980	Unclear	Unclear	No	Fair	88/60/60	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
Connor 2000	No	Yes	UMMS Small Grants Project	
Conners 1980	Unclear	Yes	NIMH and Abbott	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Atomoxetine			
Kelsey 2004 Fair	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	Age Gender Ethnicity
Atomoxetine					
Kelsey 2004 Fair	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.	Children aged 6-12 years/71% enrolled were male/ ethnicity NR.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Atomoxetine			
Kelsey 2004 Fair	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
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)
Fair	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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Atomoxetine				
Kelsey 2004 Fair	measuring vital signs, ECK's, open-ended questioning about negative physical symptoms and laboratory tests.	**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	Comorbidity
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)

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	Age Gender Ethnicity
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)	Atomoxetine: Age- mean=9.7 Gender- 98(76%) male Placebo: Age- mean=10 Gender- 103(83%) male Race: NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Spencer 2002	Mean IQ: Atomoxetine=103, placebo=106.9, p=0.021	409 screened/ 291 eligible/ 253 enrolled	59 withdrawn/ 0 lost to fu/ 253 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Spencer 2002	vital sign assessment NR for symptoms	*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%)	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Michelson 2002 Fair	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	Age Gender Ethnicity
Michelson 2002 Fair	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.	children aged 6-16 years/ 70.6% male, 29.4 female/ ethnicity NR.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Michelson 2002 Fair	**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
Michelson 2002 Fair	**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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Michelson 2002 Fair	reports from patient/parent of negative physical symptoms	**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	Comorbidity
Michelson 2001 Good	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%.

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	Age Gender Ethnicity
Michelson 2001 Good	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.	mean age 11.2 male: 71% female: 29% ethnicity NR.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Michelson 2001 Good		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.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Michelson 2001 Good	**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)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Michelson 2001 Good	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.	***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.	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
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%
Michelson2004 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%

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	Age Gender Ethnicity
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 Glocal 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.	Mean age in years: 9.66 Males = 0% Ethnicity = NR
Michelson2004 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.	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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	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
Michelson2004 2004	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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
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
Michelson2004 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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported			Total withdrawals; withdrawals due to adverse events	Comments
Biederman 2002 Subgroup Analysis of Girls from Michelson 2001	AE's reported by patients		Atom.(n=31)*	Placebo(n=21)*	3 withdrawals/ 2 due to AE's	
		Rhinitis	25.8%	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 groups)				
Michelson2004 2004	Self-report	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	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Bupriopion			
Casat, 1987 Poor	RCT, DB, parallel. Setting: one center in a four-center study	Children aged 6-12 years meeting DSM-III criteria for ADD-H and scoring >1.5 on the hyperactive factor the for the teacher's Conners questionnaire and >1.5 on the impulsive-hyperactive or restless--immature factors for the parent's Conners questionnaire. Required to weigh < 20 kg, be in good physical health, and to have normal hematological and clinical lab values as well as a normal EEG and EKG.	Conduct Disorder: 1 (10%) in placebo group, 0 in bupropion group
Connors 1996 Fair	RCT, DB, parallel. Setting: one inpatient treatment facility (n=6), rest from one out-patient university psychiatry clinic. Doctors and researches tracked a weekly log of drug administering completed by parent of patients. 6 week study.	children aged 6-12 years meeting DSM-III criteria for ADDH.	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	Age Gender Ethnicity
Bupriopion					
Casat, 1987 Poor	Bupropion hydrochloride 50mg and 75mg tabs with escalated doses based on weight (20-30kg, 30-40kg, and >40kg). Days 1-3 dose was 3mg/kg, escalated to 6mg/kg for days 15-28 with a maximum dose for the low weight group being 150mg/day, the middle weight group being 200mg/day and the high weight group being 250mg/day. OR Placebo. Administered twice a day at 7am and 7pm. This is a 6 week study.	SB 1 week placebo run-in Washout period was 14 days for all medications.	None	Brief Psychiatric Rating Scale for Children (BPRS-C); the Beitchman Children's Self-Report Psychiatric Rating Scale; the 93-item Conners Parent Symptom Questionnaire (CPSQ) and 39-item Conners Teacher Questionnaire (CTQ); and the abbreviated 10-item Conners Parent-Teacher Questionnaire. Physical exam, hematological and clinical labs, EEG, and EKG. Computerized versions of the short-term memory task (STMT) and continuous performance task (CPT). Timing NR	Mean age: bupropion=9.0 (6.8-11.5), placebo=8.4 (6.3-12.4) Males: 25 (83%) White: 24 (80%)
Connors 1996 Fair	Bupropion 3-6mg/kg/day or placebo, administered twice daily, at 7am and 7pm. This was a 6 week study.	1 week, single-blind washout.	NR	Connors parent Questionnaire, Connors Teacher questionnaire, Clinical Global Impressions-Severity Scale, Short-Term memory Test, Continuous performance Test, Physical examination, laboratory battery.	mean age 8.5 years. Males: 90% Females: 10%. Caucasian: 75%, Non-Caucasian: 25%.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Bupriopion			
Casat, 1987 Poor	NR	NR/31/30	2/0/30
Connors 1996 Fair	NR	165/NR/n =109	NR/NR/109

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Bupriopion	
Casat, 1987 Poor	Statistically significant differences between treatment groups over time: Clinical Global Impressions Scale: Severity: F=2.34, p=0.026 Improvement: F=2.61, p=0.019 CTQ Hyperactivity: F=4.98, p=0.001 Differences between treatment groups over time that are not statistically significant: CPSQ-Hyperactivity CPSQ-Conduct CTQ-Conduct
Connors 1996 Fair	**Bupropion vs placebo** Parent (observed mean scores at 28 days) (n=62 vs n=34): 13.81 vs 16.91, p-value NR; (our calculation of mean change: -5.74 vs -3.76) Teacher (observed mean scores at 28 days) (n=54 vs n=27): 14.67 vs 19.11, p-value NR; (our calculation of mean change: -5.36 vs -1.47) ANCOVA results (probability values for Treatment; Treatmentxday) 10-Item form (LOCF)-- Teacher: 0.0003, NS; Parent: NS, NS 10-Item form (observed)-- Teacher: 0.001, NS; Parent: NS, NS 39-Item Teacher Form (LOCF)-- Conduct Disorder: 0.05; NS; Hyperactivity: 0.08; NS 39-Item Teacher Form (observed)-- Conduct Disorder: 0.02, NS; Hyperactivity: 0.03, NS 93-Item Parent Form (LOCF)-- Conduct Disorder :NS, 0.01; Restless-Impulsive: NS, 0.01; Hyperactive-Immature: 0.06, NS 93-Item Parent Form (observed)-- Conduct Disorder: 0.09, 0.017; Restless-Impulsive: 0.096, 0.013; Hyperactive-Immature: 0.02, NS

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Bupriopion				
Casat, 1987 Poor	Physical exam, hematological and clinical labs, EEG, and EKG. Height and weight taken at visits. Other means of reporting adverse effects was NR.	1 (3%) subject had rash, perioral edema and agitation	2 withdrawals (1 in placebo group no reason given at day 17 and 1 in bupropion group for rash, perioral edema and agitation at day 18)	
Connors 1996 Fair	report from patient/patient's parent of negative symptoms.	no statistically significant effects on height, weight, blood pressure.	NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Daviss 2001 United States Poor	CCT Open-label Single Blind Setting: NR	Adolescent patients aged 11 to 18 years who met DSM-IV criteria for any subtype of ADHD and comorbid MDD or DD were eligible to participate. At least one parents and one teacher rating of sufficient ADHD symptomatology (≥ 6 inattentive or 6 hyperactive-impulsive symptoms rated "often" or "very often" on ARS; ≥ 6 inattentive or 6 hyperactive-impulsive symptoms rated "pretty much" or "very much" on SNAP; Attention problems T score ≥ 67 on CBCL or TRF). At least one parent OR one child rating of sufficient depressive symptomatology (Parent MFQ score ≥ 20; Child MFQ score ≥ 25; CBCL or YSR Anxious/Depressed T score ≥ 67). Psychiatrist ratings of sufficient clinical severity [CGI Severity for ADHD ≥ 4 ("moderate"), CGI Severity for depression ≥ 4 ("moderate")]	Additional diagnoses ODD=50% Specific phobia=25% Social phobia=21% Conduct disorder=21% Generalized anxiety disorder=17% Posttraumatic stress disorder=17% Panic disorder without agoraphobia=4% Separation anxiety disorder=4%

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	Age Gender Ethnicity
Daviss 2001 United States Poor	2-week single-blind placebo lead-in Buproprion vs Placebo THEN: Step 1 (visits 1 and 2): morning doses not exceeding 2 mg/kg and 100 mg Thereafter (anytime during visits 3-5) Step 2: up to 3 mg/kg qAM Step 3: up to 3 mg/kg qAM and 2 mg/kg at 5 PM Step 4: up to 3 mg/kg qAM and 3 mg/kg at 5 PM Duration: up to 10 weeks	2-week washout before enrollment; then 2-week single-blind placebo lead-in	NR	Swanson, Nolan, and Pelham (SNAP) scale Child Behavior Checklist (CBCL) Teacher's Report Form (TRF) ADHD Rating Scale Mood and Feelings Questionnaire (C-MFQ and P-MFQ)	Mean age=12.8 75% male 100% white

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Daviss 2001 United States Poor	Primary diagnosis: ADHD, combined type=58% ADHD, inattentive type=42% MDD+DD=63% DD alone=29% MDD alone=8% Previous medications tried At least one stimulant=50% At least one SSRI=25% Venlafaxine=8% Bupropion IR=4% Clonidine=4%	NR/NR/25	4 (16%) withdrawn/0 lost to fu/analyzed=24

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Daviss 2001	Bupropion SR vs placebo: visit 2 (end of placebo period)/final visit; Paired t Test, p-value (compares visit 2 and final visit)
United States	P-ARS: 28.3/17.4; 5.13, p<0.0005
	T-ARS: 28.7/23.7; 1.84, p=NS
Poor	P-MFQ: 21.6/10.0; 4.93, p<0.0005
	C-MFQ: 13.6/8.5; 2.60, p=0.016
	P-CIS: 30.4(visit 1)/18.3; 4.96, p<0.0005

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Daviss 2001 United States Poor	NR	Bupropion vs placebo in run-in phase Headaches=8% vs 8% Fatigue=4% vs 4% Nausea=8% vs 13% Rash=13% vs 4% Insomnia=4% vs 4% Irritability=8% vs 4% Tremor=4% vs 0% Motor tics=4% vs 0%	Total withdrawals: 3 (12.5%) vs 0	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Clonidine			
Singer 1995 Fair	RCT, DB, setting: john Hopkins Tourette Syndrome Clinic	Children with both Tourette's Syndrome and ADHD.	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	Age Gender Ethnicity
Clonidine					
Singer 1995 Fair	each child started with 1 capsule per day, and added 1 capsule every week to a maximum daily dose of 1 capsule 4 times per day. Subject was then maintained on the highest dose for an additional 2 weeks. Total treatment time for each agent was 6 weeks.	1 week washout between clonidine and desipramine	NR/ NR	The Child Behavior Checklist (CBCL), Gordon Diagnostic System, Clinical Evaluation of Language Function, Matching Familial Figures Test, Porteus Maze test, Restricted Academic Test, Global Linear Analogue, Tourette Syndrome Severity Scale, Hopkins Motor/Vocal Tic Scale, Leyton Obsessional Inventory-Child Version	children ages 7.2-13.6 years/ 31 male and 3 female/ 33 Caucasian and 1 African-American

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Clonidine			
Singer 1995 Fair	NR	48/37/34	3/1/1934

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Clonidine	
Singer 1995 Fair	**End-of-treatment Values: group means+/- SD: clonidine vs desipramine vs placebo** Parent linear analogues: Hyperactivity: 51.6+/-2.2 vs 32.8+/- 1.3 vs 64.4+/-0.6; Tics: 41.4=/_ 1.1 vs 30.0+/-0.7 vs 47.4+/-1.8 Mother (M)/Teacher (T) CBCL subscales: Hyperactivity (boys 6-11yrs) (M): 70.7+/-1.2 vs 68.6+/-1.4 vs 75.8+/-1.0 Nervous/overactive (boys 6-11yrs) (T): 63.7+/-0.5 vs 61.9+/-0.2 vs 69.6+/-0.2 Unpopular (boys>12y) (T): 59.0+/-0.8 vs 60.4+/-0.8 vs 65.8+/-1.8 Anxious (boys>12yrs) (T): 58.0+/-1.2 vs 56.0+/-0.2 vs 60.9+/-2.5 Obsessive-compulsive (boys>12 yrs) (T): 65.7+/-3.4 vs 60.4+/-0.9 vs 66.9+/-3.3 **Analysis of Variance for Significant Attention-Deficit Hyperactivity Disorder Variables and Drug Orthogonal Contrasts. Source: Df vs FValue vs Probability > FValue** Parent linear "hyperactivity" analogue (n=34) Drug effect: 2 vs 13.06 vs .001; Desipramine vs clonidine: 1 vs 25.26 vs .001 Order effect: 2 vs 3.62 vs .03; Drug X Order effect: 4 vs 1.15 vs NS Mother CBCL "hyperactivity", boys 6-11 yrs (n=23) Drug effect: 2 vs 4.08 vs .02; Desipramine vs clonidine: 1 vs 8.04 vs .006 Order effect: 2 vs 0.99 vs NS; Drug X Order effect: 4 vs 4.47 vs .003 Teacher CBCL "nervous/overactive", boys 6-1 yrs (n=23) Drug effect: 2 vs 4.52 vs .02; Desipramine vs clonidine: 1 vs 8.65 vs .005 Order effect: 2 vs 0.45 vs NS; Drug X Order effect: 4 vs 0.48 vs NS Teacher CBCL "unpopular", boys>12 yrs (n=8) Drug effect: 2 vs 4.91 vs .02; Desipramine vs clonidine: 1 vs 5.29 vs .04 Order effect: 2 vs 1.10 vs NS; Drug X Order effect: 4 vs 1.15 vs NS Teacher CBCL "anxious" boys>12 y (n=8) Drug effect: 2 vs 8.97 vs .002; Desipramine vs clonidine: 1 vs 16.62 vs .001 Order effect: 2 vs 11.07 vs.001; Drug X Order effect: 4 vs 6.08 vs .004 **Analysis of Variance for Significant Tic and Obsessive-Compulsive Variables and Drug Orthogonal Contrasts** Parent linear analogue for tics (n=24): Drug effect: 2 vs 3.73 vs .03; Desipramine vs clonidine: 1 vs 6.65 vs .01; Order effect: 2 vs 1.30 vs NS; Drug X order effect: 4 vs 1.70 vs NS; Teacher CBCL "obsessive-compulsive", boys>12 y (n=8): Drug effect: 2 vs 6.02 vs .01; Desipramine vs clonidine: 1 vs 11.28 vs .004; Order effect: 2 vs 11.95 vs .001; Drug X order effect: 4 vs 7.15 vs .002

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Clonidine				
Singer 1995 Fair	report from patients of negative physical symptoms	clinicians were unable to correlate drug-related adverse symptoms to clonidine or desipramine. "To date, at least 4 sudden, unexplainable deaths have occurred in children receiving this (Desipramine) medication."	NR;NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Hunt 1986 Hunt 1985 Poor	RCT, double-blind, parallel. Setting;NR	A child had to meet DSM-III criteria for ADD-H and score at least 2.0 standard deviation (s.d.) above normal on the Hyperactivity Index of the Connors Behavior Rating Scale (C-BRS) as rated by either parent or teacher. All subjects had an IQ greater than 80 and had no symptom of psychosis or primary mood disturbance. All were medically healthy with no cardiac, endocrine, or neurological disorder.	100% receiving special education services, 70% had been previously treated with stimulant medication 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	Age Gender Ethnicity
Hunt 1986 Hunt 1985 Poor	Clonidine, dosed 4 times per day, dosages increased by 0.05mg every 2 days. Clonidine was administered for 8 consecutive week-with 2 weeks baseline, and 2 weeks back to placebo (12 week study altogether).	NR	NR/ no other types of interventions used.	Connors Behavioral Ratings given by clinicians, Connors 28-Item scale for Teacher's ratings, Connors 48-Item scale for Parent's ratings, Videotaped observations done monthly, Neuromaturational assessment conducted monthly, Digit Span to test auditory attention, Kagen Matching Familiar Figures Test to measure impulsivity, visual scanning and frustration tolerance-all done by clinicians.	10 children age mean 11.6 years. Gender, ethnicity, etc NR.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Hunt 1986	NR	NR/NR/10 enrolled.	0/0/n=10
Hunt 1985			
Poor			

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Hunt	Clinicians results not rated statistically. Connors's Ratings of Teachers
1986	mean score at baseline: 49.00 +/- 5.20.
	mean score after 8 weeks of Clonidine: 25.79+/-1.31, p=.0001.
	Hyperactivity score after end of treatment: p=.001.
Hunt	Changes of conduct before vs after treatment: p=.4.
1985	Changes in inattention before vs after treatment: p=.5.
	Connor's Ratings of Parents
Poor	Overall behavioral ratings comparing pre-treatment with after 8 weeks of treatment:
	66.85+/-5.75 vs 43.00+/-6.29 (p=0.003)
	Hyperactivity Index: 2.03+/-0.16 vs 1.34+/-0.21 (p=0.004)
	Conduct Problems: 1.38+/-0.16 vs 0.99+/-0.10 (p=0.01)
	Learning Problems: 2.36+/-0.17 vs 1.53+/-0.28 (p=0.007)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Hunt 1986	reports from teachers, parents, clinicians. Blood pressure monitored.	90% (9 children) reported sleepiness in first hour after dose. Mean blood pressure decreased 10% on clonidine.	None	
Hunt 1985		10% (1 child) reported increased depressive symptoms on clonidine.		
Poor		Significant deterioration in overall behavioral during placebo withdrawal: teacher's score: (p=0.05) parent's score: (p=0.02) clinicians' score: (p=0.04)		

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Guanfacine			
Scahill 2001 United States Fair	RCT, DB, Parallel groups Patients recruited from Tic Disorders Clinic of the Yale Child Study Center	Age between 7 and 15 years, a DSM-IV diagnosis of ADHD (any type), a DSM-IV tic disorder (any type), and a score of ≥ 1.5 SDs for age and gender of the 10-item Conners hyperactivity index rated by the teacher or a parent; enrollment in the same school for at least a month before entry, with no planned change in school placements for at least 10 weeks after entry	DSM-IV tic disorders Tourette's: 20 (58.8%) Chronic motor tic disorder: 12 (35.3%)

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	Age Gender Ethnicity
Guanfacine					
Scahill 2001 United States Fair	Guanfacine vs placebo Days 1-3: single 0.5 mg dose at bedtime Days 4-7: 0.5 mg doses in the morning and at bedtime (TDD=1.0 mg) Days 8-14: 0.5 mg doses in the morning, afternoon and bedtime (TDD=1.5 mg) Days 15-28: upward adjustment to a maximum allowable dose of 4 mg/day (TID) Duration=8 weeks	Placebo washout of 7-14 days	NR	ADHD Rating Scale Clinical Global Impression global improvement score Hyperactivity index of the Parent Conners Questionnaire Yale Global Tic Severity Scale Children's Yale-Brown Obsessive Compulsive Scale Continuous Performance Test	Mean age=10.4 91.2% male 85.3% White 0.6% Black 0.6% Hispanic 0.3% Asian

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Guanfacine			
Scahill 2001 United States Fair	ADHD Rating Scale score=35.8 Parent Conners Questionnaire hyperactivity index score=17.6 Yale Global Tic Severity Scale Total Score=15.3 Body Weight=86.1 lb	50/40/34	NR/NR/34

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Guanfacine	
Scahill 2001 United States Fair	Guanfacine vs placebo ADHD Rating Scale Total Score-teacher (% mean change): -37% vs -8%, p<0.001 % patients with ratings of "much improved" or "very much improved" on CGI-I for clinical-rated change in ADHD symptoms: 9 (52.9%) vs 0, p<0.001 Total tic score of the Yale Global Tic Severity Scale (% mean change): -31% vs 0%, p=0.05 Parent-rated hyperactivity index (% mean change): -27% vs -21%, p=NS CPT Commission errors (% mean change): -22% vs +29%, p=0.01 Omission errors (% mean change); -17% vs +31%, p=0.04 ADHD rating scale-teacher (endpoint means, t-score, and p-value for comparison of endpoint means) Inattention score: 12.8 vs 15.4, t=3.79, p<0.01 Hyperactive/impulsive score: 10.8 vs 16.3, t=2.98, p<0.01

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Guanfacine				
Scahill 2001 United States Fair	Modified version of the Systematic Assessment for Treatment of Emergent Events (SAFTEE)	Total numbers of subjects reporting adverse events: Mild sedation=7 Midsleep awakening-3 Dry mouth=5 Constipation=2 Loss of appetite in the morning=2 Complaints most common in the first 4 weeks. None of these side effects was significantly more frequent in the guanfacine group than in the placebo group There were no significant change in weight from baseline to endpoint in either group and no significant difference between groups in weight change	Total withdrawals=nr Withdrawals due to adverse events: 1 (5.9%) vs 0	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
MPH ER (Metadate®)			
Greenhill 2002 Fair	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 afte	None 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	Age Gender Ethnicity
MPH ER (Metadate®)					
Greenhill 2002 Fair	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 obeservations they had kept during the run-in placebo week.	Mean age =9 years Male=81.8% White = 81.4% African American = 15.3% Hispanic = 10.2% Other = 3.5%

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
MPH ER (Metadate®)			
Greenhill 2002 Fair	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)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
MPH ER (Metadate®)	
Greenhill 2002 Fair	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.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
MPH ER (Metadate®)				
Greenhill 2002 Fair	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.	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	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
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	Age Gender Ethnicity
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)	Mean age=7.9 62.5% male 100% white

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Modafanil			
Rugino 2003 Fair	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
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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Modafanil				
Rugino 2003 Fair	NR	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	Comorbidity
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	Age Gender Ethnicity
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	Mean age=9.8 18 (60%) male Ethnicity NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroup Comorbidity: Epilepsy			
Gross-Tsur 1997 Israel Poor	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
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)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroup Comorbidity: Epilepsy				
Gross-Tsur 1997 Israel Poor	NR	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	Comorbidity
Subgroup Comorbidity: Tourette's Disorder			
Sverd 1992 Fair	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	Age Gender Ethnicity
Subgroup Comorbidity: Tourette's Disorder					
Sverd 1992 Fair	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	Mean age=8.3(1.96), range 6.1-11.9 years. Gender=11(100%) male Race: NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroup Comorbidity: Tourette's Disorder			
Sverd 1992 Fair	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
Subgroup Comorbidity: Tourette's Disorder	
Sverd 1992 Fair	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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroup Comorbidity: Tourette's Disorder				
Sverd 1992 Fair	Stimulant Site Effects Checklist (SSEC) by parents	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	Comorbidity
Subgroup Comorbidity: Mental Retardation			
Varley 1982 Fair	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%)

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	Age Gender Ethnicity
Subgroup Comorbidity: Mental Retardation					
Varley 1982 Fair	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.	Median age = 11.33 (age range: 4.58 to 15 years) Male = 70 %

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Subgroup Comorbidity: Mental Retardation			
Varley 1982 Fair	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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Subgroup Comorbidity: Mental Retardation	
Varley 1982 Fair	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.

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Subgroup Comorbidity: Mental Retardation				
Varley 1982 Fair	Parental reporting of side effects; they were given a list of common side effects. No significant side effects noted.	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	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
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%)
Gadow 1995 Fair	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%)

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	Age Gender Ethnicity
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 ScaleGlobal Tic Rating Scale	Mean age=8.3(1.96), range 6.1-11.9 years. Gender=11(100%) male Race: NR
Gadow 1995 Fair	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	Mean age=8.8(1.9), range 6.1-11.9 years. Gender=31(91.2%) male Race: NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Gadow 1992	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
Gadow 1995 Fair	NR	NR/ NR/ 34 enrolled	0/0/0

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
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)
Gadow 1995 Fair	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)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Gadow 1992	Stimulant Site Effects Checklist (SSEC) by parents	NS in SSEC * no other side effect information	none	
Gadow 1995 Fair	NR	NR	none	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Handen 1990 Fair	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	Age Gender Ethnicity
Handen 1990 Fair	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	Mean age= NR, range 6-9 years. Gender=11(91.7%) male Race: NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1990 Fair	NR	NR/ NR/ 12 enrolled	0/0/0

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Handen 1990 Fair	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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1990 Fair	Reported by teachers	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	Comorbidity
Handen 1991 Fair	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

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	Age Gender Ethnicity
Handen 1991 Fair	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	Mean age=8.6, range 6.7-12.1 years Gender=22(81.5%) male Race: NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1991 Fair	NR	NR/ NR/ 27 enrolled	13 withdrawn/ o lost to fu/ 27 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Handen 1991 Fair	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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1991 Fair	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	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	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Handen 1992 Fair	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	Age Gender Ethnicity
Handen 1992 Fair	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	Mean age=9.1, range 6-12 years Gender=10(71.4%) male Race: 6(42.9%) Africa American

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1992 Fair	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
Handen 1992 Fair	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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1992 Fair	NR	NR	none	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Handen 1994 Fair	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	Age Gender Ethnicity
Handen 1994 Fair	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,	n= 47 6.1 -12.5 years of age/31 males/ 33 Caucasians

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1994 Fair	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
Handen 1994 Fair	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)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1994 Fair		NR	NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
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

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	Age Gender Ethnicity
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.	Age (months): mean=104, range 73-149 Gender: 11(50%) male Race: 17(77%) Caucasian, 4(18%) Black, 1(5%) Hispanic

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1995	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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
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)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1995	NR	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	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
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	Age Gender Ethnicity
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	Age (months): mean=103.93, range 73-160 Gender: 23(52.3%) male Race: 32(72.7%) Caucasian, 12(27.3%) other

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1996	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
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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1996	NR	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	Comorbidity
Handen 1997 Fair	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 Fair	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.

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	Age Gender Ethnicity
Handen 1997 Fair	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.	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
Handen 1999 Fair	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.	Age: mean=4.9, range 4-5.11 years Gender: 9(82%) male Race: NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 1997 Fair	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 Fair	Mean IQ=60(11.6), range 40-78	NR/NR/11 enrolled	1 withdraw/ 0 lost/ 10 analyzed

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Handen 1997 Fair	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
Handen 1999 Fair	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)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 1997 Fair	NR	NR	NR	
Handen 1999 Fair	Parents or teachers reported	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%)	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
Handen 2000 Fair	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)
Agarwal 2001 Fair	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

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	Age Gender Ethnicity
Handen 2000 Fair	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	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
Agarwal 2001 Fair	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)	Age: 6-15 years (mean NR) Male: 8 (80%) Ethnicity: Study conducted in India, presume all children of Indian decent

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Handen 2000 Fair	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
Agarwal 2001 Fair	NR	11/11/10	0/0/10

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Handen 2000 Fair	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
Agarwal 2001 Fair	**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)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Handen 2000 Fair	Parents or teachers reported	Side Effect Checklist rated by teachers	2(16.7%)	
Agarwal 2001 Fair	NR	Drowsiness (50%), drymouth (10%), anorexia (10%), drop in systolic blood pressure (decreased by 3%-8.9%) (70%).	NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
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	Age Gender Ethnicity
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	Mean age=9 years 91% male Ethnicity 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's 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)	Mean age=8.8 years 100% male Ethnicity NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Withdrawal of Medication			
Klein 1988 Poor	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	NR	NR/NR/21	NR/NR/21

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
Withdrawal of Medication	
Klein 1988 Poor	NR
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

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Withdrawal of Medication				
Klein 1988 Poor	Height and weight were obtained routinely by secretaries in all clinic children before and after the summer with a medical scale	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	NR	

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
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

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	Age Gender Ethnicity
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.	NR

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Sleator 1974 Poor	NR	NR/NR/42	NR/NR/28

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Results
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)

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Sleator 1974 Poor	NR	NR	NR	Refer to Sprague 1973 for more details on study population? Also, FU group listed as 42, but really they only published data on 28

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Study Design Setting	Eligibility criteria	Comorbidity
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	Age Gender Ethnicity
Arnold 2004 Poor	Dexmethylphenidate 5-20mg/day Duration: 6 weeks	NA	NR	Swanson, Nolan and Pelham- ADHD scale (SNAP-ADHD) rated by parents	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%

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Arnold 2004 Poor	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
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).

Evidence Table 5. Placebo-controlled trials in children

Author Year (Quality)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Arnold 2004 Poor	reported by patients	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	Loss to follow-up: differential /high
Atomoxetine									
Kelsey 2004	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	No
Spencer 2002	NR	NR	No	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	NR
Michelson 2002	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	No
Michelson 2001 Biederman 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	No
Michelson 2004	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	No

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

Author, Year Country	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	*External Validity* Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/Washout
Atomoxetine						
Kelsey 2004	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	5-day washout
Spencer 2002	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	2-week washout
Michelson 2002	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	5-day washout
Michelson 2001 Biederman 2002	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	12-18 day washout
Michelson 2004	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	Washout of at least 5 times the plasma half-life

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

Author, Year Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Atomoxetine				
Kelsey 2004	No	Yes	Lilly	Yes
Spencer 2002	No	Yes	Lilly	Yes
Michelson 2002	No	Yes	Lilly	Yes
Michelson 2001 Biederman 2002	No	Yes	Lilly	Yes
Michelson 2004	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	Loss to follow-up: differential /high
Bupropion									
Casat 1987	NR	NR	Yes	Yes	NR	Yes	Yes	NR, NR, NR, NR	No
Connors 1996	NR	NR	Yes	Yes	Yes	Yes	Yes	NR, NR, NR, NR	Unclear
Daviss 2001 United States	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, Yes, NR	No
Poor Quality									
Clonidine									
Singer 1995	NR	Yes	NR	No	Yes	Yes	Yes	Yes, NR, NR, NR	No
Hunt 1985	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	NR
Scahill 2001	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	None

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

Author, Year Country	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	*External Validity* Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/Washout
Bupropion						
Casat 1987	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	14-day washout
Connors 1996	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	14-day washout
Daviss 2001 United States Poor Quality	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	2-week single blind placebo lead-in
Clonidine						
Singer 1995	Unclear	No	Fair	58/37/37	NR	1-week washout between periods
Hunt 1985	No	No	Poor	NR/NR/12	NR	NR/NR
Scahill 2001	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)	Placebo washout of 7· 14 days

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

Author, Year Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Bupropion				
Casat 1987	No	Yes	Burroughs-Wellcome Company	Yes
Connors 1996	No	Yes	NIMH grant; 2 authors are Glaxo-Wellcome scientists	Yes
Daviss 2001 United States	No	Yes	Glaxo-Wellcome	Yes
Poor Quality				
Clonidine				
Singer 1995	No	Yes	Tourette Syndrome Association and US	
Hunt 1985	No	Yes	NR	
Scahill 2001	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	Loss to follow-up: differential /high
Greenhill 2002	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	No
Rugino 2003	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	None

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

				External Validity		
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/Washout**
Greenhill 2002	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).	1-week SB placebo washout - excluded any that responded to placebo during these phase
Rugino 2003	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	NR/NR

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

Author, Year Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Greenhill 2002	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	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	Loss to follow-up: differential /high
Gross-Tsur 1997	Non-random assignment. Methods for assignment NR	NA	n/a-crossover	Yes	NR	Yes	Yes	NR, NR, NR, NR	Unclear
Tourette's Disorder									
Sverd 1992	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR	Unclear
Mental Retardation									
Varley 1982	NR	NR	NR	Yes	NR	Yes	Yes	Yes, NR, NR, NR	No/No
Gadow 1992	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR	Unclear

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

Author, Year Country	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	*External Validity* Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/Washout
Gross-Tsur 1997	Yes	No	Poor	NR/NR/30	NR	NR/NR
Tourette's Disorder						
Sverd 1992	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	NR/NR
Mental Retardation						
Varley 1982	Yes	No	Fair	15/10/10	Psychotic disorders, undersocialized aggressive conduct disorders	NR/NR
Gadow 1992	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	NR/NR

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

Author, Year Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Gross-Tsur 1997	NR	Yes	NR	Yes for epilepsy+ADHD populations
Tourette's Disorder				
Sverd 1992	No	Yes	NR	Yes
Mental Retardation				
Varley 1982	80% naïve	Yes	NR	
Gadow 1992	Unclear	Yes	Tourette Syndrome Association and NIMH grants; CIBA supplied MPH and placebo	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	Loss to follow-up: differential /high
Gadow 1995	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR	Unclear
Handen 1990	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR	Unclear
Handen 1991	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR	Unclear
Handen 1992	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR	Unclear

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

Author, Year Country	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	*External Validity* Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/Washout
Gadow 1995	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	NR/NR
Handen 1990	Unclear	No	Fair	NR/NR/12	NR	NR/NR
Handen 1991	Unclear	No	Fair	NR/NR/27	Severe motor deficits; use of other medication (anticonvulsants, antipsychotics); diagnosis of major depression or psychosis	NR/NR
Handen 1992	Unclear	No	Fair	NR/NR/14	NR	NR/NR

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

Author, Year Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Gadow 1995	Unclear	Yes	Tourette Syndrome Association and NIMH grants; CIBA supplied MPH and placebo	
Handen 1990	Unclear	Yes	Edith L. Trees Foundation and Research Advisory Committee of Children's Hospital of Pittsburgh	Yes
Handen 1991	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	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	Loss to follow-up: differential /high
Handen 1994	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR	Unclear
Handen 1995	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR	Unclear
Handen 1996	NR	Inadequate - hospital pharmacist	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR	Unclear
Handen 1997	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	No
Handen 1999	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	No
Handen 2000	NR	NR	NR	Yes	Yes	Yes	Yes	NR, NR, NR, NR	Unclear
Agarwal 2001	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	No

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

Author, Year Country	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	*External Validity* Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/Washout
Handen 1994	Unclear	No	Fair	NR/NR/47	NR	NR/NR
Handen 1995	Yes	No	Fair	NR/NR/22	Diagnosis of autism or pervasive developmental disorder	NR/NR
Handen 1996	Yes	No	Fair	NR/NR/44	Autism or pervasive developmental disorder	NR/NR
Handen 1997	Unclear	No	Fair	NR/NR/52	Autism or pervasive developmental disorder	NR/NR
Handen 1999	No	No	Fair	NR/NR/11	Autism or pervasive developmental disorder	NR/NR
Handen 2000	Yes	No	Fair	NR/NR/13	NR	NR/NR
Agarwal 2001	Yes	No	Fair	NR/NR/10	NR	NR/NR

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

Author, Year Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Handen 1994	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 1995	No	Yes	National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation	
Handen 1996	No	Yes	National Institute of Child Health and Human Development; US DHHS	
Handen 1997	No	Yes	National Institute of Child Health and Human Development; US DHHS	
Handen 1999	No	Yes	Fanny Pushin Rosenberg Research Foundation	
Handen 2000	Unclear	Yes	Fanny Pushin Rosenberg Research Foundation	
Agarwal 2001	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	Loss to follow-up: differential /high
Withdrawal of medication									
Klein 1988	NR	NR	Yes	Yes	NR	Unblinded study	Unblinded study	Yes, NR, NR, NR	None
Zeiner 1999 Fair	NR	NR	NR	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	No
Sleator 1974	n/a - nonrandomized	n/a - nonrandomized	NR	Yes	NR	Yes	Yes	NR, NR, NR, NR	NR
Arnold 2004 Poor	NR	NR	No	Yes	Yes	Yes	Yes	Yes, NR, NR, NR	No

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

				External Validity		
Author, Year Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/Washout**
Withdrawal of medication						
Klein 1988	No	No	Poor	NR/NR/62	NR	NR/NR
Zeiner 1999 Fair	Yes	No	Fair	NR/NR/21	NR	NR/NR
Sleator 1974	NR	NR	Poor	NR/NR/42	NR	NR/NR
Arnold 2004 Poor	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	NR/NR

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

Author, Year Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Withdrawal of medication				
Klein 1988	NR	Yes	Supported in part by Public Health Service grant MH 18579	Yes
Zeiner 1999 Fair	Unclear	Yes	Norwegian Medical Research Council, Norwegian Public Health Association, and the Legacy of Haldis and Josef	Yes
Sleator 1974	NR	Yes	NIMH grant; MPH supplied by Ciba-Geigy	
Arnold 2004 Poor	Unclear	Yes	Celgene	

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Eligibility criteria	Comorbidity	Interventions and total daily dose Duration Dosing schedule
Placebo-Controlled Trials (>/= 6 Months Duration)			
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/ enrolled	Number withdrawn/ lost to fu/
Placebo-Controlled Trials (>/= 6 Months Duration)				
DEX				
Conrad 1971 (Poor)	NR NR NR	NR	1350/262/106/68	NR

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Results
Placebo-Controlled Trials (>/= 6 Months Duration)	
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 due
Placebo-Controlled Trials (>/= 6 Months Duration)			
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/ enrolled	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 due
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/ enrolled	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 due
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-Drug Treatment			
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 -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 treatmer 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/ enrolled	Number withdrawn/ lost to fu/
ADHD Drug Versus Non-Drug Treatment				
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-Drug Treatment	
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 advantage 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 due
ADHD Drug Versus Non-Drug Treatment			
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/ enrolled	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 due
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"

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Age Gender Ethnicity	Other population characteristics (mean scores)	Number screened/ eligible/ enrolled	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

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 treatment at 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 (R_c^2) 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).

Evidence Table 7. Long-term efficacy trials

Author Year (Quality)	Method of adverse effects	Adverse Effects Reported	Total withdrawals; withdrawals due
Brown 1985	NR	NR	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
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

					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**
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	Yes
Brown 1985	NR/NR	NR	Yes	NR	Yes
Kupietz 1987	NR/NR	NR	Yes	NIMH grant MH 36004	Yes
Ialongo 1993	NR/NR	NR	Yes	NR	Yes

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	Yes
Firestone 1986	NR/NR	NR	Yes	Ontario Ministry of Health grants	Yes

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	Allowed other medications/ interventions
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	NR
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	NR

NR = Not reported

Evidence Table 9. Head to Head Trials in Adults with ADHD

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Bupropion SR vs methylphenidate				
Kuperman, 2001 U.S. (Fair)	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	Mean years of education: 15.2	NR/NR/37 N enrolled in each group not reported
Dextroamphetamine vs guanfacine				
Taylor, 2001 U.S. (Fair)	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	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

NR = Not reported

Evidence Table 9. Head to Head Trials in Adults with ADHD

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/ analyzed
Bupropion SR vs methylphenidate	
Kuperman, 2001 U.S. (Fair)	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
Dextroamphetamine vs guanfacine	
Taylor, 2001 U.S. (Fair)	No withdrawals; No loss to followup; 17 analyzed, all exposed to both DAMP & guanfacine

NR = Not reported

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)
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

NR = Not reported

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	Comments
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	
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	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.

NR = Not reported

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	Allowed other medications/ interventions
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	NR

NR = Not reported

Evidence Table 9. Head to Head Trials in Adults with ADHD

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Dextroamphetamine vs modafinil				
Taylor, 2000 U.S. (Fair)	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	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

NR = Not reported

Evidence Table 9. Head to Head Trials in Adults with ADHD

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/ analyzed
Dextroamphetamine vs modafinil	
Taylor, 2000 U.S. (Fair)	1 withdrawn 0 lost to fu; 21 analyzed, all exposed to both DAMP & modafinil

NR = Not reported

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

NR = Not reported

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	Comments
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	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.

NR = Not reported

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	Allowed other medications/ interventions
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	NR

NR = Not reported

Evidence Table 9. Head to Head Trials in Adults with ADHD

Author Year Country Trial Name (Quality Score)	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Dextroamphetamine vs methyphenidate				
Matochik, 1994 U.S. (Fair)	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	**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 = Not reported

Evidence Table 9. Head to Head Trials in Adults with ADHD

Author Year Country Trial Name (Quality Score)	Number withdrawn/ lost to fu/ analyzed
Dextroamphetamine vs methyphenidate	
Matochik, 1994 U.S. (Fair)	NR/NR/ 37 analyzed: methyphenidate: n=19 DAMP: n=18

NR = Not reported

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 Crying: NR; NR vs 0.1; 0.04 Being sad: NR; NR vs 0.1; 0.04

NR = Not reported

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	Comments
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	

NR = Not reported

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

Author, Year Country	Internal Validity: Reporting of attrition, crossovers, adherence, and contamination	Internal Validity: Loss to follow-up: differential / high	Internal Validity: Intention-to-treat (ITT) analysis	Internal Validity: 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

Author, Year Country	*External Validity* 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)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Amphetamine mixture			
Spencer, 2001 U.S. (Fair)	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			
Michelson, 2003 31 outpatient sites in North America, country not otherwise specified (Fair)	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)	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

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
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
Atmoxetine		
Michelson, 2003 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
Wernicke, 2004 U.S. (Fair)	Visits at weekly intervals assessed CAARS, HAM-D, HAM-A	NR NR NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Amphetamine mixture			
Spencer, 2001 U.S. (Fair)	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.	3 (10%) withdrawals; 0% lost to fu; 27 (90%) analyzed. N per drug not reported
Atmoxetine			
Michelson, 2003 31 outpatient sites in North America, country not otherwise specified (Fair)	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	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)
Wernicke, 2004 U.S. (Fair)	Not reported	NR/NR/380 Atomoxetine with abrupt discontinuation n=90; Atomoxetine with tapered discontinuation n=94; Placebo n=196	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)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Amphetamine mixture	
Spencer, 2001 U.S. (Fair)	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	

Michelson, 2003 31 outpatient sites in North America, country not otherwise specified (Fair)	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)

Wernicke, 2004 U.S. (Fair)	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.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported
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)
Atmoxetine		
Michelson, 2003 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)
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)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Amphetamine mixture		
Spencer, 2001 U.S. (Fair)	Adderall vs placebo: Total withdrawals: 0 vs 3 (10%) Withdrawals due to AEs not reported	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		
Michelson, 2003 31 outpatient sites in North America, country not otherwise specified (Fair)	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)	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	Depressive or anxiety symptoms did not significantly increase following drug discontinuation.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Atmoxetine			
Spencer, 1998 U.S. (Fair)	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
Bupropion			
Wilens, 2001 U.S. (Fair)	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
Dexamphetamine			
Paterson, 1999 Australia (Fair)	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

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
Atmoxetine		
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.
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
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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Atmoxetine			
Spencer, 1998 U.S. (Fair)	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	1 withdrawn/ 0 lost to fu 21 analyzed Tomoxetine: n=11 Placebo: n=10
Bupropion			
Wilens, 2001 U.S. (Fair)	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	2 (5%) withdrawn; 0% lost to fu; 40 (100%) analyzed: Bupropion n=21, Placebo n=19
Dexamphetamine			
Paterson, 1999 Australia (Fair)	51% were inattentive type 46.7% were combined inattentive and hyperactive types 2% were hyperactive type	68/51/45 24 dexamphetamine 21 placebo	1 (2.2%) withdrawn 0% lost to followup 45 (100%) analyzed: Dexamphetamine n=24, Placebo n=21

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Atmoxetine	
Spencer, 1998 U.S. (Fair)	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
Bupropion	
Wilens, 2001 U.S. (Fair)	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
Dexamphetamine	
Paterson, 1999 Australia (Fair)	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)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported
Atmoxetine		
Spencer, 1998 U.S. (Fair)	self-report from patients	no serious adverse events observed, 1 subject withdrawn after becoming ery anxious on tomoxetine.
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)
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)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Atmoxetine		
Spencer, 1998 U.S. (Fair)	tomoxetine: 1/21 (due to increased anxiety in patient) placebo: 0 withdrawals;	3 week study period.
Bupropion		
Wilens, 2001 U.S. (Fair)	Bupropion vs placebo, Total withdrawals: 2 (9.52%, noncompliance) vs 0% Due to AEs: 0 vs 0	
Dexamphetamine		
Paterson, 1999 Australia (Fair)	Dexamphetamine vs placebo, Total withdrawals: 1 (4.2%) vs 0% Due to AEs: 1 (4.2%, depression) vs 0%	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.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Methylphenidate			
Bouffard, 2003 Canada (Fair)	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
Cox, 2000 U.S. (Fair)	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

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
Methylphenidate		
Bouffard, 2003 Canada (Fair)	2 self-rating questionnaires (CAARS & AAPBS); SCL-90, BDI, HAM-A; GAF	Mean age 34 80% male Ethnicity NR
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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Methylphenidate			
Bouffard, 2003 Canada (Fair)	Mean IQ 101	93/NR/38 Same subjects exposed to both treatments	8 (21%) withdrawn Loss to followup NR 30 (79%) analyzed, same subjects exposed to both treatments (phases were combined in analysis)
Cox, 2000 U.S. (Fair)	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	0% withdrawn; 0% loss to followup; 13 (100%) analyzed, same subjects exposed to both treatments (phases were combined in analysis)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Methylphenidate	
Bouffard, 2003 Canada (Fair)	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)
Cox, 2000 U.S. (Fair)	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)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported
Methylphenidate		
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)
Cox, 2000 U.S. (Fair)	NR	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Methylphenidate		
Bouffard, 2003 Canada (Fair)	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.	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).
Cox, 2000 U.S. (Fair)	Methylphenidate vs placebo, Total withdrawals: 0 vs 0 Withdrawals due to AEs: 0 vs 0	Data from the first treatment phase was not reported separately. Author concludes that Ritalin improved ADHD driving performance to the non-ADHD level.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Gualtieri, 1985 U.S. (Fair)	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

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
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)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Gualtieri, 1985 U.S. (Fair)	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	NR/NR/8 N per drug not reported (phases were combined in analysis).

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Gualtieri, 1985 U.S. (Fair)	

	Placebo	MPH	P-value
AAS	27.7	25.8	ns
ZSDS	45.3	37.5	ns
ZSAS	38.3	33.8	ns
CPT correct	121.8	128.5	< 0.05
CPT errors	5.3	2.1	ns
Actometer	98.6	60.3	ns
Growth hormone	1.3	6.0	ns

MPH significantly improved correct responses on the CPT.

All subjects accurately guessed the active drug condition

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported
Gualtieri, 1985 U.S. (Fair)	NR	AEs were not reported among the 8 subjects who participated in the short-term DB RCT.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Gualtieri, 1985 U.S. (Fair)	Methylphenidate vs placebo, Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0	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.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Methylphenidate			
Kinsbourne, 2001 U.S. (Fair)	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
Levin 2002 U.S. (Fair)	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
Methylphenidate		
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
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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Methylphenidate			
Kinsbourne, 2001 U.S. (Fair)	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	0% withdrawn 0% lost to followup 17 (100%) analyzed; N per drug not reported (phases were combined in analysis)
Levin 2002 U.S. (Fair)	NR	NR/NR/40 Placebo patch + placebo pill, n=10 Nicotine, n=10 Methylphenidate, n=10 Nicotine + methylphenidate, n=10	6 (15%) withdrawn/lost to fu nr/34 analyzed (placebo n=7, nicotine n=9, MPH n=9, combination n=9)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Methylphenidate	
Kinsbourne, 2001 U.S. (Fair)	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
Levin 2002 U.S. (Fair)	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
Methylphenidate		
Kinsbourne, 2001 U.S. (Fair)	NR	NR
Levin 2002 U.S. (Fair)	NR	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Methylphenidate		
Kinsbourne, 2001 U.S. (Fair)	Methylphenidate (5/10/20 mg/day) vs placebo, Total withdrawals: 0/0/0 vs 0. Withdrawals due to AEs: 0/0/0 vs 0	Data from the first treatment phase was not reported separately.
Levin 2002 U.S. (Fair)	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)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Mattes, 1984 U.S. (Fair)	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
Methylphenidate			
Schubiner, 2002 U.S. (Fair)	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

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
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
Methylphenidate		
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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Mattes, 1984 U.S. (Fair)	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	5 (7.6%) withdrawn; Loss to followup NR; 61(92.4%) analyzed; N per drug not reported (phases were combined in analysis).
Methylphenidate			
Schubiner, 2002 U.S. (Fair)	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)	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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Mattes, 1984 U.S. (Fair)	No response to methylphenidate occurred in either patients with or without childhood ADHD. Results among patients without childhood ADHD were not 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)
Methylphenidate	
Schubiner, 2002 U.S. (Fair)	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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported
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		
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%) Stare a lot or daydream=12 (50%) vs 17 (71%) Anxious=19 (79%) vs 15 (63%)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Mattes, 1984 U.S. (Fair)	Methylphenidate vs placebo: Total withdrawals unclear by treatment group; Withdrawals due to AEs not reported.	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.
Methylphenidate		
Schubiner, 2002 U.S. (Fair)	Methylphenidate vs placebo: Total withdrawals: 13 (54.2%) vs 10 (41.7%) Withdrawals due to adverse events: 0 vs 1 (4.2%)	Comorbid for cocaine dependence Pemoline arm dropped (n=11) due to low enrollment after 1 year

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Spencer, 1995 U.S. (Fair)	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
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
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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Spencer, 1995 U.S. (Fair)	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.	2 (8%) withdrawn 0% lost to followup 23 (92%) analyzed. N per drug in 1st treatment phase not reported.
Spencer, 2005 U.S. (Poor)	38% major depression 9% multiple (>2) anxiety disorders	289/NR/146 104 in MPH; 42 in placebo	36/NR/110 26(25%) in MPH; 10(24%) in placebo dropout

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Spencer, 1995 U.S. (Fair)	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)	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
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)
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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Spencer, 1995 U.S. (Fair)	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%	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)	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)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Methylphenidate			
Tenenbaum, 2002 U.S. (Fair)	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

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
Methylphenidate		
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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Methylphenidate			
Tenenbaum, 2002 U.S. (Fair)	Not reported	128/85/33 Same subjects exposed to all treatments.	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).

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Methylphenidate	
Tenenbaum, 2002 U.S. (Fair)	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]

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported
Methylphenidate		
Tenenbaum, 2002 U.S. (Fair)	NR	NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Methylphenidate		
Tenenbaum, 2002 U.S. (Fair)	Methylphenidate vs placebo: Total withdrawals unclear by treatment group. Withdrawals due to AEs 0 vs 0	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.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Wood, 1976 (Fair)	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,
Modafinil			
Turner, 2004 U.K. (Fair)	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
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)
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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Wood, 1976 (Fair)	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	0/0/11 analyzed: N NR
Modafinil			
Turner, 2004 U.K. (Fair)	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	Withdrawn NR Lost to followup NR 20 (100%) analyzed Analysis of 1st treatment phase included 10 in modafinil, 10 in placebo

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Wood, 1976 (Fair)	**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
Modafinil	
Turner, 2004 U.K. (Fair)	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
Wood, 1976 (Fair)	self-report, results on questionnaire data	No adverse effects reported, no response to meds: n=1
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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Wood, 1976 (Fair)	0/0	
Modafinil		
Turner, 2004 U.K. (Fair)	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)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Wender, 1985 U.S. (Fair)	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

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
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

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Wender, 1985 U.S. (Fair)	Comorbidities: 68% dysthymic disorder 22% cyclothymic disorder	NR/NR/37 Same subjects exposed to both treatments	0% withdrawn; 0% lost to followup; 37 (100%) analyzed, N per drug not reported (phases were combined in analysis).

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Wender, 1985 U.S. (Fair)	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)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported
Wender, 1985 U.S. (Fair)	Self-report	Mild anxiety, insomnia, jaw tension, tooth grinding, overstimulation, irritability, nose tingling

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Wender, 1985 U.S. (Fair)	Methylphenidate vs placebo: Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0	Data from the first phase was not reported separately. Outcomes were presented as combined data from phases of each drug.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Pemoline			
Wender, 1981 U.S. (Fair)	Pemoline or placebo was dispensed in identical 37.5 mg tablets. Initial dose was 18.75 mg, and increased by this amount every 3 to 7 days, based on patient's response. Maximum daily dose was set at 4 tablets = 150 mg/day. The entire daily dose was given once per day in the morning. Pemoline mean dose 71 mg/day Placebo mean dose 101 mg/day Duration 6 weeks	NR/NR	NR
Wilens, 1999 U.S. (Fair)	Pemoline or placebo (in 18.75 and 37.5 mg capsules) were prescribed in once-daily doses. Study medication was titrated up to 1 mg/kg/day by end of week 1, to 2 mg/kg/day by week 2, and to 3 mg/kg/day by week 3. Pemoline mean dose at end of week 4: 2.2 mg/kg/day (148 mg/day). Placebo mean dose NR. Duration 10 weeks: two 4-week treatment periods separated by 2-week washout. Treatment order was randomized	Run-in NR; 2-week washout between 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
Pemoline		
Wender, 1981 U.S. (Fair)	Baseline characteristics were determined using WAIS, SCL-90, Minnesota Multiphasic Personality Inventory; GAS; WRAT (assess reading, spelling, & arithmetic skills), Lincoln-Oseretsky Test (a battery of motor tasks that assesses coordination); Porteus Maze; Embedded Figures Test; Physicians' Global Assessment of Change; Physicians' Global Rating of Change "Baseline characteristics were determined using WAIS, SCL-90, Minnesota Multiphasic Personality Inventory; GAS; WRAT (assess reading, spelling, & arithmetic skills), Lincoln-Oseretsky Test (a battery of motor tasks that assesses coordination); Porteus Maze; Embedded Figures Test; Physicians' Global Assessment of Change; Physicians' Global Rating of Change Patient's clinical status was evaluated over the course of the trial using 3 instruments: 1) The Medicine Response Sheet 2) The Physician Target Symptom Scale 3) The Physicians' Global Assessment of Change Presence of hyperactivity in childhood was assessed by parents using PRS.	Mean age 28.3 46% female Ethnicity NR
Wilens, 1999 U.S. (Fair)	ADHD Symptom Checklist; CGI Severity & Improvement. Improvement defined as 30% reduction in symptoms. Neuropsychologic test battery was administered three times: at baseline and after each arm of the study, and included an auditory version of the CPT, the Stroop test, the computerized WCST, the scattered letters version of the visual cancellations test, and the ROCFT.	Mean age 40.7 68.6% male Ethnicity NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Pemoline			
Wender, 1981 U.S. (Fair)	Mean GAS rating 56 (moderately severe psychopathology) Other diagnoses, number of subjects: Alcohol abuse: 6 Drug abuse: 6 Brquet's syndrome: 2 probable Antisocial personality: 3 definite, 4 probable Generalized anxiety disorder: 13 definite, 2 probable Dysphoric disorders: 21 patients All but one of the female subjects had dysphoric disorders, and half had alcoholic fathers. Among the patients' 34 children, 41% had been independently identified as hyperactive.	NR/60/48 Pemoline n=26 Placebo n=22	6 (12.5%) withdrawn; Lost to followup NR; 47 (98%)analyzed: 26 subjects had PRS scores >=12 indicating childhood symptoms, and were considered true hyperactives. In the subsample (n=26) of true hyperactives: Pemoline n=17 Placebo n=9
Wilens, 1999 U.S. (Fair)	All subjects had at least one previous comorbid psychiatric disorder; for 57% the comorbid disorder was also present within the past month. Comorbid disorders (lifetime) Antisocial disorder 17% Major depression 40% Dysthymia 15% Bipolar disorder 0% Multiple anxiety disorders 28% Social phobia 29% Generalized anxiety disorder 15% Bulimia 3% Obsessive-compulsive disorder 0% Smoking 40% Alcohol abuse or dependence 59% Drug abuse or dependence 59%	151/35/35 N per drug in 1st phase not reported	8 (23%) withdrawn Lost to followup NR 35 (100%) analyzed; N per drug not reported (phases were combined in analysis)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Pemoline	
Wender, 1981 U.S. (Fair)	Physicans' Global Assessment of Change: % of all 48 patients (with or without childhood symptoms), pemoline vs placebo, p-values not reported: +3 (marked improvement) = 23 vs 18% +2 (moderate improvement) 15 vs 14% +1 (mild improvement) 27 vs 14% <0 (worsening) 35 vs 55% The following results are among true (childhood-onset) hyperactives (pemoline n=17; placebo n=9): +3 = 29.4 vs 0% +2 = 17.6 vs 11.1% +1 = 17.6 vs 0% 0 (no change) = 17.6 vs 66.7% -1 (mild worsening) = 17.6 vs 11.1% -2 (moderate worsening) = 0 vs 11.1% Change in Physicians' Global Assessment, pemoline vs placebo: High score on PRS: -0.1 vs +1.25 (ns) Low score on PRS: +1.15 vs +1.35 (ns) Change in target-symptom ratings, pemoline vs placebo: Motor hyperactivity -0.94 vs -0.11 (p=0.05) Attentional difficulties -0.64 vs 0.11 (p=0.05) Affective liability -0.53 vs -0.33 (ns) Inability to complete tasks -0.78 vs -0.22 (ns) Hot temper -1.18 vs -0.11 (p<0.05) Impaired interpersonal relationships -0.59 vs 0 (ns) Impulsivity -0.88 vs 0.34 (p=0.001) Stress intolerance -0.77 vs 0.12 (p=0.01)
Wilens, 1999 U.S. (Fair)	Pemoline vs placebo: Change in DSM-III-R ADHD symptoms checklist score: -7.5 vs -1 (p=0.015) % of subjects who improved by 30% reduction in symptoms: 50% vs 17% (p=0.008) CGI Improvement score of 1 or 2 (much to very much improved), by timepoint: Week 1: 7% vs 9% (ns) Week 2: 24% vs 3% (p<=0.06) Week 3: 33% vs 21% (ns) Week 4: 38% vs 14% (p<=0.05) Reduction in ADHD symptoms at endpoints, week 4 and 10, p-value signifying change from baseline: 28% (p=0.0001) vs 10% (ns) Neuropsychologic test results: no difference between pemoline and placebo in the aggregate or on the individual tests, including CPT, Stroop, WCST, scattered letters version of the visual cancellations test, and ROCFT. Results not shown.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported
Pemoline		
Wender, 1981 U.S. (Fair)	Elicited by investigator in an open-ended fashion	54% in pemoline and 1 in placebo complained of moderate to severe side effects N subjects in pemoline group, : Headache n=7 Abdominal symptoms (nausea, cramping, anorexia) n=5 Insomnia n=6 Anxiety n=2 Intensification of symptoms n=1 Confusion and depersonalization n=1 Prodromal psychosis with loosening of associations, increased anxiety, and possible ideas of reference =1. 1 subject on pemoline showed increased lactic dehydrogenase levels for 4 months and a marked decrease in polymorphic leukocyte counts for another 4 months
Wilens, 1999 U.S. (Fair)	% of patients who experienced at least one adverse effect, pemoline vs placebo: 24% vs 12% ($p<0.0006$) SGOT analyses to assess liver function were performed at baseline and at end of weeks 4 and 10.	On pemoline: Mandibular joint 17% Dry mouth 14% Dysphoria 8% Decreased appetite 8% 12 on pemoline and 4 on placebo had dose lowered because of AEs One patient developed a mild tic that persisted at 1-year follow-up

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Pemoline		
Wender, 1981 U.S. (Fair)	Pemoline vs placebo, Total withdrawals: 5 (19%) vs 1 (4.5%) Withdrawals due to AEs: 4 (15.4%) vs 0%	This study enrolled adults with ADD symptoms, irrespective of childhood onset. The report provides separate results of the subsample of patients who were considered true hyperactives based on parent rating scale.
Wilens, 1999 U.S. (Fair)	Pemoline vs placebo, Total withdrawals: 4 (11.4%) vs 3 (8.6%); 1 (2.9%) treatment NR Withdrawals due to AEs: 4 (11.4%) vs 0%	Data from the first phase was not reported separately. An order-effects analysis found no significant order effect.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Interventions (drug, regimen, duration)	Run-in/ Washout Period	Allowed other medications/ interventions
Wilens, 1999 U.S. (Fair)	Pemoline or placebo (in 18.75 and 37.5 mg capsules) were prescribed in once-daily doses. Study medication was titrated up to 1 mg/kg/day by end of week 1, to 2 mg/kg/day by week 2, and to 3 mg/kg/day by week 3. Pemoline mean dose at end of week 4: 2.2 mg/kg/day (148 mg/day). Placebo mean dose NR. Duration 10 weeks: two 4-week treatment periods separated by 2-week washout. Treatment order was randomized	Run-in NR; 2-week washout between 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
Wilens, 1999 U.S. (Fair)	ADHD Symptom Checklist; CGI Severity & Improvement. Improvement defined as 30% reduction in symptoms. Neuropsychologic test battery was administered three times: at baseline and after each arm of the study, and included an auditory version of the CPT, the Stroop test, the computerized WCST, the scattered letters version of the visual cancellations test, and the ROCFT.	Mean age 40.7 68.6% male Ethnicity NR

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled N per drug	Number withdrawn/ lost to fu/ analyzed: N per drug
Wilens, 1999 U.S. (Fair)	All subjects had at least one previous comorbid psychiatric disorder; for 57% the comorbid disorder was also present within the past month. Comorbid disorders (lifetime) Antisocial disorder 17% Major depression 40% Dysthymia 15% Bipolar disorder 0% Multiple anxiety disorders 28% Social phobia 29% Generalized anxiety disorder 15% Bulimia 3% Obsessive-compulsive disorder 0% Smoking 40% Alcohol abuse or dependence 59% Drug abuse or dependence 59%	151/35/35 N per drug in 1st phase not reported	8 (23%) withdrawn Lost to followup NR 35 (100%) analyzed; N per drug not reported (phases were combined in analysis)

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Results
Wilens, 1999 U.S. (Fair)	Pemoline vs placebo: Change in DSM-III-R ADHD symptoms checklist score: -7.5 vs -1 (p=0.015) % of subjects who improved by 30% reduction in symptoms: 50% vs 17% (p=0.008) CGI Improvement score of 1 or 2 (much to very much improved), by timepoint: Week 1: 7% vs 9% (ns) Week 2: 24% vs 3% (p<=0.06) Week 3: 33% vs 21% (ns) Week 4: 38% vs 14% (p<=0.05) Reduction in ADHD symptoms at endpoints, week 4 and 10, p-value signifying change from baseline: 28% (p=0.0001) vs 10% (ns) Neuropsychologic test results: no difference between pemoline and placebo in the aggregate or on the individual tests, including CPT, Stroop, WCST, scattered letters version of the visual cancellations test, and ROCFT. Results not shown.

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported
Wilens, 1999 U.S. (Fair)	% of patients who experienced at least one adverse effect, pemoline vs placebo: 24% vs 12% (p<0.0006) SGOT analyses to assess liver function were performed at baseline and at end of weeks 4 and 10.	On pemoline: Mandibular joint 17% Dry mouth 14% Dysphoria 8% Decreased appetite 8% 12 on pemoline and 4 on placebo had dose lowered because of AEs One patient developed a mild tic that persisted at 1-year follow-up

Evidence Table 11. Placebo-controlled trials in adults with ADHD

Author Year Country (Quality Score)	By treatment, total withdrawals; withdrawals due to adverse events	Comments
Wilens, 1999 U.S. (Fair)	Pemoline vs placebo, Total withdrawals: 4 (11.4%) vs 3 (8.6%); 1 (2.9%) treatment NR Withdrawals due to AEs: 4 (11.4%) vs 0%	Data from the first phase was not reported separately. An order-effects analysis found no significant order effect.

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?**
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
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
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

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity				
Author, Year	**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**
Bouffard, 2003	Yes NR NR NR	No/ no	No: 79%	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
Mattes, 1984	Yes NR NR NR	No/ no	No: 92%	No	Fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity	
Author, Year	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
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)
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
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).

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
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
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
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.

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?**
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
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, 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

	Internal Validity				
Author, Year	**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**
Michelson, 2003	Yes NR NR NR	No/ no	No: 96%	No	Fair
Paterson, 1999	Yes Yes Yes Yes	No/ no	Yes	No	Fair
Schubiner, 2002	Yes NR NR NR	NR	Yes	No	Fair
Spencer, 1995	Yes NR NR NR	No/ no	No: 92%	No	Fair
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

	External Validity	
Author, Year	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
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.
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, 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
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
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, 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?**
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
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
Wender, 1981	Method NR	Method NR	Not reported	Yes	Yes but method not described	Not reported	Yes but method not described

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity				
Author, Year	**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**
Spencer, 2001	Yes NR NR NR	No/ no	No: 90%	No	Fair
Spencer, 2005	Yes NR NR NR	NR	No	No	Poor
Tenenbaum, 2002	Yes NR Yes NR	No/ no	No: 72.7%	No	Fair
Turner, 2004	Yes NR NR NR	No/ no	Yes	No	Fair
Wender, 1981	Yes NR NR NR	No/ no	Unclear	No	Fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity	
Author, Year	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
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.
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.
Wender, 1981	NR/60/48 Pemoline n=26 Placebo n=22	Excluded DSM-III diagnoses of schizophrenia, schizoaffective disorder, primary affective disorder, schizotypal personality, or "borderline" personality; excluded organic brain syndrome and mental retardation. Excluded patients who reported that they had taken stimulant medication or "diet pills" in the past and that they had been stimulated, excited, or "wired" by such medication. Excluded gravid or lactating females. Excluded medical contraindications to stimulant drug therapy.

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
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
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
Wender, 1981	NR/NR	No	Yes	Abbott Laboratories; 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?**
Wender, 1985	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes	NR	Yes
Wernicke, 2004	Method NR	Method NR	Not reported	Yes	Yes	NR	Yes but method not described
Wilens, 1999	Method NR	Method NR	Not reported by phase; same subjects exposed to both treatments	Yes	Yes	Yes	Yes
Wilens, 2001	Method NR	Method NR	Yes	Yes	Yes	NR	Yes
Wood, 1976	Method NR	Method NR	Same 11 subjects in both drug groups	Yes	NR	NR	Yes but method not described

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	Internal Validity				
Author, Year	**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**
Wender, 1985	Attrition yes	No/ no	No	No	Fair
Wernicke, 2004	Yes NR NR NR	No/ no	No: 99.2%	No	Fair
Wilens, 1999	Yes NR NR NR	No/ no	Yes	No	Fair
Wilens, 2001	Yes NR NR NR	No/ no	Yes	No	Fair
Wood, 1976	NR NR NR NR	No/ no	Yes	No	Fair

Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

	External Validity	
Author, Year	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Wender, 1985	NR/NR/37 Same subjects exposed to both treatments	Excluded DSM-III diagnoses of schizophrenia or schizoaffective disorder, current major mood disorder, and any specific features of schizoid, schizotypal, or borderline personality disorder, such as unstable and intense interpersonal relationships with idealization and devaluation, identity disturbances, intolerance of being alone, and physically self-damaging acts, including self-mutilation and suicidal gestures.
Wernicke, 2004	NR/NR/380; Atomoxetine with abrupt discontinuation n=90; Atomoxetine with tapered discontinuation n=94; Placebo n=196	Not reported
Wilens, 1999	151/35/35 N per drug in 1st phase not reported	Potential subjects were excluded if they had any clinically significant chronic medical conditions or clinically significant abnormal baseline laboratory liver function tests, mental retardation (IQ <75), organic brain disorders, clinically unstable psychiatric conditions, bipolar or psychotic disorders, drug or alcohol abuse or dependence within the 6 months preceding the study, previous exposure to pemoline, or current use of psychotropics. Also excluded pregnant or nursing women.
Wilens, 2001	154/NR/40 Bupropion n=21 Placebo n=19	Potential subjects were excluded if they had any clinically significant chronic medical conditions or clinically significant abnormal baseline laboratory liver function tests, mental retardation (IQ <75), organic brain disorders, clinically unstable psychiatric conditions, bipolar or psychotic disorders, drug or alcohol abuse or dependence within the 6 months preceding the study, or current use of psychotropics. Potential subjects with previous exposure to bupropion were also excluded.
Wood, 1976	NR/25/15	After first screening for inclusion, subjects who met the diagnosis of schizophrenia or primary affective disorders according to the Research Diagnostic Criteria of Spitzer were excluded.

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
Wender, 1985	Run-in NR; 1-week washout between treatment phases	No	Yes	NIMH grant	Yes
Wernicke, 2004	NR/NR	No	Yes	Eli Lilly	Yes
Wilens, 1999	Run-in NR; 2-week washout between treatment phases	No, but excluded previous use of trial drug	Yes	Abbott Laboratories; NIH Scientist Development Award	Yes
Wilens, 2001	NR/NR	No, but excluded previous use of trial drug	Yes	Glaxo Wellcome Inc.; NIH; National Institute on Drug Abuse	Yes
Wood, 1976	Run-in NR; no washour between phases of the crossover trial since MPH has "a short duration of action"	NR	Yes	NR	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 fu 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 fu 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

Evidence Table 13. Observational Studies - Functional Outcomes

Author Year Country	Assessment Techniques	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu 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

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 <u>Teacher reports of below grade level work (% children):</u> 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 <u>Other</u> 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

Evidence Table 13. Observational Studies - Functional Outcomes

Author Year Country	Design	Eligibility Criteria	Duration	Interventions (mean dose)	Concomitant medication
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 fu Analyzed
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
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 fu 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 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?
Functional capacity					
Paternite 1999	No: excluded 24 (19.8%)	n/a	Yes	Yes	NR
Weiss 1975	No	NR	Yes	No	No
Lerer 1977	No: excluded 11 (41%) nonresponders	n/a	Yes	Yes	No
Hecktman 1984	Yes	No	Yes	Yes	Yes No
Charles 1981	No: excluded 36 (36.7%)	n/a	No	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?	Overall quality rating
Functional capacity						
Paternite 1999	Yes	Yes	Yes	Yes	Yes	Fair
Weiss 1975	Yes	No	Unclear	NR	Yes	Fair
Lerer 1977	Yes	No	Unclear	NR	Yes	Fair
Hecktman 1984	Yes	No	Unclear	No	Yes	Fair
Charles 1981	No	No	No	No	Yes	Fair-Poor

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?
Persistence					
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
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
Bussing 2005	Yes	n/a	Yes	Yes	No

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?	Overall quality rating
Persistence						
Lage 2004	Yes	Yes	Yes	Yes	Yes	Fair
Marcus 2005	Yes	Yes	Yes	Yes	Yes	Fair
Bussing 2005	Yes	Yes	Yes	Yes	Yes	Fair

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Design	Eligibility Criteria	Duration	Interventions (mean dose)
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	Tomoxetine mean dose nr

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Elementary School Children - Atomoxetine (tomoxetine)					
Kratochvil 2001 U.S. (Fair)	NR	Weight measured at weekly clinic visits	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	Comments
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	Design	Eligibility Criteria	Duration	Interventions (mean dose)
Elementary School Children - Methylphenidate				
Brehaut 2003 Canada (Fair)	British Columbia Linked Health Dataset (BCLHD)	January 1, 1990 and December 31, 1996	NR	Methylphenidate (mean dose NR)

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Elementary School Children - Methylphenidate					
Brehaut 2003 Canada (Fair)	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	1,028,028 exposed Eligible NR Selected=1,026,873		

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country | **Safety Outcomes** | **Comments**

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	Design	Eligibility Criteria	Duration	Interventions (mean dose)
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	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

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Gadow 1999 U.S. (Fair)	NR	Height Weight Tics	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	Comments
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	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	Interventions (mean dose)
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	Methlyphenidate mean daily dose of 20.56 mg Imipramine mean daily dose of 65.4 mg

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Quinn 1975 U.S. (Fair)	NR	Height Weight Seizures	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	Comments
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	Design	Eligibility Criteria	Duration	Interventions (mean dose)
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	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

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Mattes 1983 U.S. (Fair)	Thioridazine hydrochloride received by 34 (39.5%) at some time during the study	Changes in weight and height percentiles	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** | **Comments**

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)

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	Interventions (mean dose)
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	Atomoxetine maximum dosage of 2 mg/kg/day administered in two divided doses (mean dose nr)

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Wernicke 2003 U.S. (Fair)	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	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	Comments
Wernicke 2003 U.S. (Fair)		

Baseline and change in corrected (Fridericia formula) QT intervals: short-term treatment

	Children/adolescents			Adults		
	Atomoxetine (n=325)	Placebo (n=202)	p-value	Atomoxetine (n=257)	Placebo (n=257)	p-value
QTcD						
Mean change at endpoint	-3.1	-4.4	NS	+0.6	+0.8	NS
Increase≥30 msec [no. (%)]	7 (2.2%)	9 (4.5%)	NS	6 (2.3%)	9 (3.5%)	NS
Increase≥60 msec or ≥500 msec: None for children/adolescents or adults						
QTcB						
Mean change at endpoint	+1.5	-4.5	0.004	+5.7	+0.6	<0.001
Increase≥30 msec [no. (%)]	20 (6.2%)	15 (7.4%)	NS	16 (6.2%)	12 (4.7%)	NS
Increase≥60 msec [no. (%)]	1 (0.3%)	2 (1.0%)	NS	0	0	NS
Increase≥500 msec None for children/adolescents or adults						
QTcF						
Mean change at endpoint	-5.3	-4.4	NS	-2.7	+0.9	0.008
Increase≥30 msec [no. (%)]	6 (1.8%)	5 (2.5%)	NS	3 (1.2%)	7 (2.7%)	NS
Increase≥60 msec or ≥500 msec: None for children/adolescents or adults						

Long-term treatment group: "There is no evidence of an increase in QTc with increasing dosage of atomoxetine as indicated by lack of a dose effect (p=0.792)." data nr

Number of patients with treatment-emergent cardiovascular adverse events (%)

	Children/adolescents			Adults		
	Atomoxetine (n=340)	Placebo (n=207)	p	Atomoxetine (n=269)	Placebo (n=263)	p
Palpitations	1 (0.3%)	0	NS	10 (3.7%)	2 (0.8%)	0.037
Tachycardia	3 (0.9%)	0	NS	4 (1.5%)	2 (0.8%)	NS
Cardiac murmur	2 (0.6%)	0	NS	0	0	NA
Extrasystoles	0	0	NA	1 (0.4%)	1 (0.4%)	NS
Sinus tachycardia	2 (0.6%)	0	NS	1 (0.4%)	0	NS
Ventricular extrasystole	1 (0.3%)	0	NS	0	0	NA
Atrial hypertrophy	0	0	NA	0	1 (0.4%)	NS
Sinus bradycardia	0	0	NA	0	1 (0.4%)	NS

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Design	Eligibility Criteria	Duration	Interventions (mean dose)
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.	Methylphenidate mean dose 34 mg/day, n=60 Dextroamphetamine mean dose 16.5 mg/day, n=24 (Imipramine/desipramine, n=16)

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Gross 1976 U.S. (Fair)	NR	Changes in weight and height percentiles, compared with Iowa city norms	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

Comments

Gross
1976
U.S.
(Fair)

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.

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	Interventions (mean dose)
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	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

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Safer 1972 U.S. (Fair)	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.	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

Safer
1972
U.S.
(Fair)

Safety Outcomes

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.

Comments

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	Interventions (mean dose)
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	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

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Satterfield 1979 U.S. (Good)	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.	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

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.

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	Interventions (mean dose)
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	Methylphenidate mean daily doses: 12-month cohort: 24.1 mg 24-month cohort: 29.1 mg Dosing schedule NR

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
McNutt 1976a (preliminary report) McNutt 1976b U.S. (Fair)	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	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	Comments
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	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	Interventions (mean dose)
Wilens 2003 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	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

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Wilens 2003 U.S. (Fair)	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.	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

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

Comments

Wilens 2003 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	Interventions (mean dose)
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	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.
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)	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
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	DEX MPH Unmedicated controls Mean dosages NR

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Gualtieri 1985 U.S. (Fair)	Not reported	Monthly clinic visits, NOS.	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)	NR	Measurements of height and weight were made by the author at the times of initial neurologic examination and at re-examination during treatment	Mean age nr 100% male Race NR	NR/NR/36	NR NR NR
Safer 1973 U.S. (Fair)	NR	School nurses completed a form based on review of school health records	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	Comments
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	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	Interventions (mean dose)
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	Medicated (MPH 23 mg) vs unmedicated
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	MPH: 27mg/day, range 10-60mg dextroamphetamine 12mg/day, range 5-20mg

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Zeiner 1995 Norway (Fair)	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.	mean age 9.0 yrs 100% male Ethnicity NR	36/25/23	0/0/23 analyzed
Safer 1975 (Poor)	NR	the height and the weight were recorded by two independent examiners	Mean age: 10.3 years, range 8-13 years Gender: 80% male 100% Caucasian	66/NR/NR	NR/NR/26

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Safety Outcomes	Comments
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	

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Design	Eligibility Criteria	Duration	Interventions (mean dose)
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	MPH or pemoline Mean dosages 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	MPH 10.3 mg
Adults				
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	Adderall (modal dose 10 mg - bid dosing)

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Elementary School Children - Stimulants (combined therapy)					
Rao 1998 U.S./Canada (Fair)	NR	Information from case report forms	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)	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)	Mean age=8.8 years 81% male Race NR	NR NR 16 patients/16 controls	NR NR 16 patients/16 controls
Adults					
Horrigan 2000 U.S. (Fair)	SSRI (sertraline or venlafaxine) in 4 patients	Motor tic	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	Comments
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	
Adults		
Horrigan 2000 U.S. (Fair)	Motor tic: 1/24 (4%)	

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Design	Eligibility Criteria	Duration	Interventions (mean dose)
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	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

Evidence Table 15. Observational Studies - Long-term Safety

Author Year Country	Concomitant medication	Safety Assessment	Age Gender Ethnicity	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed
Preschool children					
Ghuman 2001 U.S. (Fair)	Psychotropic medications (unspecified) for mood disorders, anxiety disorders, and obsessive-compulsive disorder	Clinic notes of Side Effects Rating Form (SERF) ratings	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	Comments
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 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
Quinn 1975	No	Yes	No	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	
Quinn 1975	NR	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?
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	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
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	NR	Yes	Fair	Study selected for MPH responders, decreasing likelihood of AEs.
Zeiner 1995	Yes	Yes	Fair	