Drug Class Review

Pharmacologic Treatments for Attention Deficit Hyperactivity Disorder

Final Update 4 Evidence Tables

December 2011

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The literature on this topic is scanned periodically.

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

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Abbreviations used in evidence tables

Abbreviation	Term
ACDS	ADHD Clinical Diagnostic Scale
ADDB-Inv	Investigator-rated Attention Deficit and Disruptive Behavior Disorder Instrument
ADHD	Attention deficit hyperactivity disorder
ADHD-AM-RS	Attention Deficit Hyperactivity Disorder - Rating Scale (morning version)
ADHD-RS-IV	Attention Deficit Hyperactivity Disorder - Rating Scale IV
AISRS	Adult ADHD Investigator Symptom Rating Scale
ASQ	Abbreviated Symptom Questionnaire
bid	Twice daily
BMI	Body mass index
BPM	Beats per minute
CCT	Controlled clinical trial
CD	Conduct disorder
CGAS	Children's Global Assessment Scale
CGI	Clinical global impression
CGI-I	Clinical global impression-Improvement
CHQ	Child Health Questionnaire
CI	Confidence interval
CLON	Clonidine
CMTD	Chronic multiple tic disorder
CNS	Central nervous system
CPRS-48	Connors' Parent Rating Scale
CPRS-R:L	Conners' Parent Rating Scale-Revised: Long Form
CR	Controlled release
CTRS-39	Connors' Teacher Rating Scale
CTRS-L	Conners' Teacher Rating Scale-Long Form
CTRS-R	Connors' Teacher Rating Scale-Revised
CV	Cardiovascular
CVS	Cardiovascular system
d	Day
DB	Double-blind
DBD-NOS	Disruptive behavior disorder behavior, not otherwise specified
DBP	Diastolic blood pressure
DEX	Dextroamphetamine
DICA	Diagnostic Instrument of Childhood and Adolescence
dL	Deciliter
d-MPH	Dexmethylphenidate
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Ejection fraction
ER	Extended release
FDA	US Food and Drug Administration
FU	Follow-up
g	Gram
GAD	Generalized anxiety disorder

Abbreviation	Term
GAF	Global Assessment of Functioning
GI	Gastrointestinal
GP	General practitioner
GTRS	Global Tic Rating Scale
h	Hour
HARS	Hamilton Anxiety Rating Scale
HDL-C	High density lipoprotein cholesterol
HDRS	Hamilton Depression Rating scale
HMO	Health maintenance organization
HR	Hazard ratio
HRQOL	Health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
IQ	Intelligence quotient
IQR	Interquartile range
IR	Immediate release
ITT	Intent-to-treat
K-SADS-PL	Kiddie-SADS- Present and Lifetime Diagnostic Interview
L	Liter
LA	Long acting
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last Observation Carried Forward
LS means	Least squares means
MANCOVA	Multivariate analysis of covariance
MAS	Mixed Amphetamine Salts
mcg	Microgram
mg	Milligram
min	Minute
mL	Milliliter
mo	Month
MPH	Methylphenidate
MPH MR	Methylphenidate modified release
MTS	Methylphenidate transdermal formulation
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NCBRF-TIQ	Nisonger Child Behavior Rating Form
NR	Not reported
NS	Not significant
NSD	No significant difference
OCD	Obsessive-compulsive disorder
ODD	Oppositional Defiant Disorder
OR	Odds ratio
OROS	Osmotic release oral system
P	*P* value
P	Placebo
PCT	Placebo-controlled trial

Abbreviation	Term
PDD-NOS	Pervasive developmental disorder, not otherwise specified
PERMP-A	Permanent Product Measure of Performance-Attempted
PERMP-C	Permanent Product Measure of Performance-Correct
PGA	Parent Global Assessment
PPY	Per person year
qd	Once daily
QOL	Quality of life
RCT	Randomized controlled trial
RR	Relative risk
SAD	Separation Anxiety Disorder
SAERS	Barkeley Dtimulant Adverse Event Rating Scale
SB	Single-blind
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SKAMP-A	Swanson, Kotkin, Agler, M-Flynn and Pelham-Attention
SKAMP-D	Swanson, Kotkin, Agler, M-Flynn and Pelham-Deportment
SNAP	Swanson Nolan and Pelham Rating Scale-Revised
SR	Sustained release
SSEC	Stimulant Side Effects Checklist
SUD	Substance Use Disorder
tid	Three times daily
URTI	Upper respiratory tract infection
VAS	Visual analog scale
vs.	Compared with (versus)
WD	Withdrawal
WURS	Wender Utah Rating Scale
XR	Extended release
y	Year
YGTSS	Yale Global Tic Severity Scale
YQOL-R	Youth Quality of Life-Research Version

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Amiri 2008 Iran	Patients were 6-15 years old who met the DSM-IV-TR diagnostic criteria for ADHD. They had total and/or subscale scores on ADHD-RS-IV, school version at least 1.5 SD above norms for patient's age and gender. Patients were excluded if they had a history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders; any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk and mental retardation; they had a clinically significant chronic medical condition, including organic brain disorder, seizures and current abuse or dependence on drugs within 6 months; hypertension, hypotension and habitual consumption of more than 250mg/day of caffeine.	Modafinil Dependant on weight: 200mg/day for <30 kg and 300mg/day for >30 kg Methylphenidate Dependant on weight: 20mg/day for <30 kg and 30mg/day for >30 kg	NR	Mean age: 9.2 years (Modafinil) vs 8.96 years (Methylphenidate) 78.3% male 100% Persian	NR	60	5 withdrew: 2 from modafinil group vs 3 from methylphenidate group Lost to FU=NR Analyzed=60

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Amiri 2008 Iran	Modafinil vs Methylphenidate Change in Parent ADHD-RS-IV from baseline at day 42: -24.36 vs -22.66 % of responders based on Parent ADHD-RS-IV: 73.33% vs 70% Change in Teacher ADHD-RS-IV from baseline at day 42: -20.53 vs -21.33 % of responders based on Teacher ADHD-RS-IV: 73.33% vs 73.33%	Modafinil vs Methylphenidate Abdominal pain: 4 vs 7 Anxiety, nervousness: 3 vs 4 Decreased appetite: 18 vs 26 (p=0.03) Sadness: 4 vs 6 Difficulty falling asleep: 2 vs 8 (p=0.05) Weight loss: 3 vs 7 Nausea: 2 vs 4 Dry mouth: 7 vs 10 Irritability: 4 vs 6 Headaches: 4 vs 7	5 withdrew: 2 from modafinil group and 3 from methylphenidate group Withdrawals due to AEs: NR	Tehran University of Medical Sciences	

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Arnold 1978/Huestis 1975 (Fair)	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; insufficient benefit from an initial 2-week "placebo washout" to be maintained without active drug	Days 1/2/3+: Dextroamphetamine: 5/10/15 mg Methylphenidate: 10/20/30 mg 3 weeks, then crossover Twice daily: morning and noon	NR	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	29	NR NR 29

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Arnold 1978/Huestis 1975 (Fair)	Mean changes on (p=NS for all): Conners' school behavior checklist by teachers: -21.26 vs -17.97 Sum of first 6 items on Davids' Hyperkinetic Rating Scale by teacher: -6.65 vs -5.89 Item 7 (poor schoolwork) on Davids' Hyperkinetic Rating Scale by teachers: -0.69 vs -0.79 First six items on Davids' Hyperkinetic Rating Scale by parents: -5.45 vs -5.35 Problem checklist by parents: -43.1 vs -37.79 Psychiatrists' ratings of parent-assessed target symptoms: -1.87 vs -1.62	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 Tummy aches: -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	Grant from Ohio Department of Mental Health and Mental Retardation; matched dosage forms were furnished by Ciba-Geigy Pharmaceutical Corp.	

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Barkley 2000 (Poor)	DSM-IV criteria for ADHD	Adderall 10 mg and 20 mg Methylphenidate 10 mg and 20 mg Placebo 1 week, then crossover Twice daily: morning and noon	NR	n=35 Mean age=14 85.7% male Race NR	Mean IQ=103.9	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

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

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Barrickman 1995 US (Fair)	Diagnosis of ADHD (DSM-III-R) and be between 7 and 17 years old	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 Methylphenidate 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 third 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	NR	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	18	3 (16.7%) withdrawn/0 lost to fu/15 analyzed

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Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Barrickman 1995 US (Fair)	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	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	NR	Significant treatment order effects were reported

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Bergman 1991 US (Poor)	DSM-III diagnosis of Attention Deficit Disorder with Hyperactivity (ADDH)	Sustained-release methylphenidate 20 mg (single morning dose) Short-acting (regular) methylphenidate 10 mg (twice daily - morning and afternoon) Placebo 1 day	NR	Mean age NR (between 6 and 12) 100% male Ethnicity NR	NR	42	NR/NR/NR
Biederman 2006 StART substudy (Wigal 2005)	Subgroup of girls from Wigal 2005. See for eligibility criteria	See Wigal 2005	See Wigal 2005	Mean age=8.7 years Subgroup of 100% girls 59.1% white 22.8% black 17.5% Hispanic 1.8% Asian/pacific islander 8.8% other	Mean weight (lb): 71.98 ADHD subtype Hyperactive/impulsive: 0% Combined: 100%	57	NR/NR/57
Biederman 2007 US	Children 6-12 years old with DSM-IV-TR diagnosis of combined or predominantly hyperactive-impulsive subtype of ADHD. History of treatment with a stable regiment of stimulant medication, ability to follow classroom instructions, and functioning at age-appropriate academic levels	Lisdexamfetamine dimesylate (LDX) Mixed amphetamine salts extended-release (MAS XR) - reference arm Initial dose: 10mg/day	NR	Mean age: 9.1 years 63.5% male 55.8% White 23.1% Black 15.4% Hispanic 5.8% other	100% ADHD-combined subtype Mean age of ADHD onset: 5.8 years Mean time since diagnosis: 3.3 years Prior treatment Amphetamine: 44.2% Methylphenidate: 26.9% Stimulant NOS: 11.5% Stimulants with Atomoxetine: 9.6% Other: 1.9% Not listed: 5.8%	52	2 withdrew 1 was lost to follow-up 50 analyzed

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Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Bergman 1991 US (Poor)	SR methylphenidate = short-acting methylphenidate on all measures (data NR)	NR	NR NR	NIMH Grants (MH 38838-05 and MH 30906-09)	
Biederman 2006 StART substudy (Wigal 2005)	MAS XR vs atomoxetine SKAMP scale mean changes Deportment: -0.48 vs -0.04; p<0.001 Attention: -0.45 vs -0.05; p<0.001 Math problems (mean number) Attempted: 135.27 vs 119.72; p<0.04 Completed correctly: 94.4% vs 96%; NS	MAS XR vs atomoxetine (p-values NR) Appetite decrease: 40.7% vs 12.5% Upper abdominal pain: 29.6% vs 15.6% Insomnia: 25.9% vs 3.1% Headache: 14.8% vs 9.4% Weight decrease: 7.4% vs 0 Anorexia: 7.4% vs 6.3% Nausea: 3.7% vs 12.5% Vomiting: 3.7% vs 15.6% Somnolence: 3.7% vs 28.1% Fatigue: 0 vs 6.3% Any adverse event: 78% vs 66%	Overall withdrawals: NR AE withdrawals: 7% vs 3%	See Wigal 2005	
Biederman 2007 US	**LS Mean SKAMP-DS scores at endpoint** LDX: 0.8 vs Placebo: 1.7 (p<0.0001) MAS XR: 0.8 vs Placebo: 1.7 (p<0.0001) **LS Mean SKAMP-AS scores at endpoint** LDX: 1.2 vs Placebo: 1.8 (p<0.0001) MAS XR: 1.2 vs Placebo: 1.8 (p<0.0001) **LS Means PERMP-A scores** LDX: 133.3 vs Placebo: 88.2 (p<0.0001) MAS XR: 133.6 vs Placebo: 88.2 (p<0.0001) **LS Means PERMP-C scores** LDX: 129.6 vs Placebo: 84.1 (p<0.0001) MAS XR: 129.4 vs Placebo: 84.1 (p<0.0001) **CGI-I scale at endpoint** LDX: 2.2 vs Placebo: 4.2 (p<0.0001) MAS XR: 2.3 vs Placebo: 4.2 (p<0.0001)	AEs occurring at an incidence of ≥ 2% during the double-blind period were: **LDX** Insomnia: 8% Decreased appetite: 6% Anorexia: 4% Upper respiratory infection: 2% **MAS XR** Decreased appetite: 4% Upper abdominal pain: 4% Upper respiratory infection: 2% Vomiting: 2% Insomnia: 2% **Placebo** Vomiting: 4% Insomnia: 2% Upper abdominal pain: 2%	2 withdrew 1 withdrew due to viral gastroenteritis	New River Pharmaceuticals and Shire Development Inc	

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Borcherding 1990 (Poor)	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	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.	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	46	1 (2.2%) withdrawn/lost to fu NR/# analyzed ranged by outcome

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Borcherding 1990 (Poor)	Efficacy NR	Abnormal movements Abnormal movements "NOTED": 34/45 (76%) overall Abnormal movements "OBSERVED": 27/34 (79%) Of those n=27 subjects (Dextroamphetamine vs methylphenidate; p=NS on all): Abnormal movements: 6 (22%) vs 10 (37%) Orofacial movements: 7 (27.9%) vs 7 (27.9%) Stereotypies: 2 (7.4%) vs 4 (14.8%) Compulsive behaviors Overall: 23/45 (51.1%) Of those 23 subjects (Dextroamphetamine vs methylphenidate; p=NS on all): Compulsive behaviors: 13 (56%) vs 5 (22%); p=0.09 STESS items (mean scores) Does things over & over a certain number of times before they seem quite right (n=38): 0.4 vs 0.4; both > placebo Meticulous; pays close attention to detail: 0.4 vs 0.3; both > placebo Overly neat and clean: 0.2 vs 0.1: only dextroamphetamine > placebo Has trouble making up his mind: 0.4 vs 0.5; methylphenidate > placebo Jerks/twitches or unusual movements: 0.2 vs 0.2; both = placebo CPRS items (mean scores) (all "both > placebo) Compulsive 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	NR	Compares results of this 100% female trial to trial of 45 boys (Castellanos 1996)

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Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Castellanos 1997 US Subgroup of Elia 1991	(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 Tourette's syndrome	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; BID at 9 am and 1 pm; individualized curriculum and instruction provided from 9am to 12:30pm in a highly structured classroom, including a positive reinforcement management program using play money (paid for appropriate behavior and fined for inappropriate behavior).	Haloperidol	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	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

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

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Castellanos 1997 US Subgroup of Elia 1991	Tic severity Dextroamphetamine had greater severity than placebo (+25%), p<0.05 Methylphenidate severity indistinguishable from placebo (-4%), p=NS	# cases with dextroamphetamine vs methylphenidate (denominate unclear) Marked appetite suppression with transient weight loss: 4 vs 3 Initial insomnia: 10 vs 2 Transient obsessive-compulsive symptoms: 1 vs 5	NR NR	NR	NIMH Research Day Program

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Chronis 2003/Pelham 1999a (Fair)	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Chronis 2003/Pelham 1999a (Fair)	1) Placebo/Placebo/Placebo 2) MPH .3/.3/.3 3) MPH .3/.3/.15 4) MPH .3/Placebo/Placebo 5) Adderall .3/Placebo/.3 6) Adderall .3/Placebo/.15 7) Adderall .3/Placebo/Placebo All p-values reflect comparison to condition #1 (Placebo/Placebo/Placebo) Positive affect (all p=NS): 1) 28.1; 2) 30.81; 3) 29.17; 4) 29.40; 5) 30.28; 6) 30.29; 7) 29.62 Negative affect (all p=NS): 1) 12.51; 2) 11.43; 3) 12.67; 4) 12.22; 5) 11.90, 6) 11.68, 7) 11.79 Parent task completion (all p=NS): 1) 2.34; 2) 1.94; 3) 2.18; 4) 2.29; 5) 2.25; 6) 1.95; 7) 2.37 Child task completion: 1) 2.46; 2) 1.61, **p<0.01**; 3) 2.47; 4) 2.17; 5) 1.78; 6) 1.77, **p<0.01**; 7) 2.17 Overall effectiveness: 1) 2.52; 2) 1.90, **p<0.01**; 3) 2.27; 4) 2.19; 5) 2.07; 6) 1.75, **p<0.001**; 7) 2.22 Pleasantness of interaction: 1) 2.76; 2) 1.65, **p<0.01**; 3) 2.41; 4) 2.26, **p<0.01**; 5) 1.67, **p<0.01**; 6) 1.44, **p<0.001**; 7) 1.98, **p<0.01**	See Pelham 1999a	See Pelham 1999a	See Pelham 1999a	

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Conners 1980	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.	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	Age: 7.9 years (range 6-11 years) Male: 57 (95%) White: 59 (98%) African-American: 1 (2%)	NR	60	NR/NR/60

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Conners 1980	**Pemoline vs MPH vs Placebo** CPT-- For Week 0 Total trials: N=15 vs N=15 vs N=16 For Week 0 all others: N=16 vs N=16 vs N=16; For Week 8 all categories: N=18 vs N=19 vs N=17 *Total Trials:* 3.75 (327.47-323.72) vs 8.72 (331.40-322.68) vs -0.44 (324.50-324.94) *Total signals:* 0.12 (50.12-50.00) vs 0.12 (50.12-50.00) vs 0 (50.00-50.00) *Total responses,:* -9.1 (52.12-61.22) vs -7.04 (62.38-69.42) vs 7.82 (68.88-61.06) *Correct responses:* -6.44 (27.62-34.06) vs -10.62 (28.75-39.37) vs -2.09 (30.44-32.53) *Errors of omission:* 4.36 (20.75-16.39) vs 9.36 (21.31-11.95) vs 0.97 (19.56-18.59) *Errors of commission:* 1.00 (22.44-21.44) vs 4.84 (27.31-22.47) vs 9.47 (34.00-24.53) Parent Questionnaire Factors-- For Week 0: N=19 vs N=20 vs N=21; For Week 8: N=18 vs N=20 vs N=20 *Conduct problem:* 0.37 (1.14-0.77) vs 0.52 (1.16-0.64) vs 0.17 (1.00-1.17) *Anxiety:* 0.23 (0.64-0.41) vs 0.40 (0.89-0.49) vs 0.09 (0.70-0.61) *Impulsivity:* 0.54 (1.21-0.70) vs 0.84 (1.53-0.69) vs 0.14 (1.45-1.31) *Immaturity:* 0.32 (0.67-0.35) vs 0.30 (0.73-0.43) vs 0.15 (0.79-0.64) *Psychosomatic:* 0.20 (0.37-0.17) vs 0.18 (0.46-0.28) vs 0.15 (0.40-0.25) *Obsessional:* -0.18 (0.39-0.57) vs 0.20 (0.77-0.57) vs 0.07 (0.60-0.53) *Antisocial:* 0.16 (0.22-0.06) vs 0.16 (0.24-0.08) vs 0.09 (0.20-0.11) *Hyperactivity:* 0.39 (0.80-0.41) vs 0.53 (0.99-0.46) vs 0.23 (0.98-0.75) Teacher Questionnaire Factors-- For Week 0: N=19 vs N=20 vs N=21; For Week 8: N=16 vs N=19 vs N=19 *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)	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	NIMH and Abbott	

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Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Connor 2000 US (Poor)	Children aged 6-16 years meeting DSM-III-R criteria for ADHD and either Aggressive Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD) with 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.	A: 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) B: Methylphenidate maximum, flexibly titrated based on clinical efficacy and reported side effects, of 40 mg twice daily (mean dose 32.5 mg/d) Titration periods at 1, 2, and 3 months time periods where dosage assessments were conducted. Duration of study: 3 months.	All were free of medication at baseline.	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 had a previous treatment history with any other psychiatric medication.	24	0/0/24

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Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Connor 2000 US (Poor)	Clonidine only vs Methylphenidate only **Parent Ratings** No interaction was found to be significant for group X time. **Teachers Ratings** SSQ Number of Problem Settings 7.3 at month 3 vs 3.1 at month 3 (p= 0.009) APRS Group receiving MPH only was significantly improved at all time points in comparison to the clonidine only group (p=0.02). Time point values NR. **Laboratory Scores** GPB Marginally significant finding for time score for non-dominant hand in clonidine only group (F= 2.50, p=0.068). Time point values NR. No significant effects were found for non-dominant hand number of errors. 1.0 errors at 2 months and 3 months vs 0.1 errors at 2 months and 0.23 errors at 3 months for number of errors for dominant hand performance. This was significant, but P value NR. Marginally significant effect for clonidine group with slower completion times with the dominant hand than the MPH group (F=2.22, p=0.052).	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.	Clonidine vs Methylphenidate Total withdrawals: 2 (25%) vs 1 (12.5%) Due to AE: 0 (0%) vs 1 (12.5%)	UMMS Small Grants Project Award	

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Cox 2004 (Fair)	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	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	NR	Mean age =17.2 100% male Race NR	Inattentive type=4(66.7%) Combined type=2(33.3%) Proportion taking medication for ADHD at baseline NR Mean baseline dose of MPH NR	7	1 (14.3%) withdrawn/0 lost to fu/analyzed=6

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

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Cox 2004 (Fair)	OROS Methylphenidate vs methylphenidate TID IDS 2 PM: -0.55 vs -0.54, p=NS 5 PM: -2.2 vs -1.04, p=NS 8 PM: -1.98 vs 4.23, p=0.01 11 PM: -1.65 vs 5.1, p=???? (wrote to author - reported as 0.1 in text but I think that's wrong) Individual parameters (F-value/p-value for MPH TID vs MPH OROS) Standard deviation steering: F=0.65, p=0.42 Off Road: 2.50/0.12 Veering across midline: 2.11/0.15 Inappropriate braking: 4.47/0.04 % missed stop signals: 5.76/0.02 % bumps: 1.35/0.25 % crashes: 3.13/0.08 Speeding: 1.60/0.21 Standard deviation speed: 4.19/0.04 Risky Driving Means (daily driving diaries - self reported): 2.6 vs 3.2, p=NS	NR	1 (14.3%) withdrawals 0 due to adverse events	McNeil Consumer and Specialty Pharmaceuticals	

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Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Cox 2006	Male and female active drivers who had ADHD and were aged 16 to 19 years were eligible to participate in the study. To be included in the study, adolescents had to have a diagnosis of current ADHD as determined by parent report, questionnaire, and structured clinical interviews; a positive history of stimulant responsiveness as disclosed by adolescents and parent reports; and current license to drive and reported daily driving activity. Adolescents were excluded when they had a history of tics or any adverse reactions to stimulant medication, a history of substance abuse disclosed by patient or parent, or a coexisting medical condition or medication usage that is known to interfere with the safe administration of stimulant medications.	OROS MPH, se-AMPH ER, or placebo Days 1 through 5, a half dose (36 mg/day OROS MPH or 15 mg/day se-AMPH ER), and on days 6 to 17, the full study dose of active drug (72 mg/day of OROS MPH or 30 mg/day of se-AMPH ER).	21 were taking MPH , and 12 were taking amphetamine formulations.	Mean Age 17.8 yrs Gender: 54% male Ethnicity: NR	Medication before study No medication 2 MPH formulations 21 Amphetamine formulations 12	35	35 analyzed
Dopfner 2004 Germany Designed as a non-inferiority trial	Children between 8 and 15 years who met ICD-10 diagnosis of Hyperkinetic Disorder (F90) of a DSM-IV diagnosis of ADHD using a diagnostic checklist, DCL-HKS. All patients were methylphenidate responders on the basis of clinical assessment. They also had to have an intelligence IQ ≥85 and a body weight >20 kg.	Medikinet-Retard (methylphenidate ER) qd Methylphenidate IR (MPH IR) bid Placebo Dosage varied: 9 patients (11%) received 10 mg/d; 54 (68%) patients received 20 mg/d; 14 patients (17%) received 30 mg; and 2 patients (3%) received 40mg.	NR	Mean age: 10.0 yrs Gender: 89.9% male Ethnicity NR	Mean IQ: 103.0 (+/- 10.4) DSM-IV diagnosis of ADHD Combined type: 92.4% Predominately inattentive: 7.6%	82	3/ NR/ 79

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Cox 2006	Overall driving performance was better with active treatment. a significant medication effect vs. placebo (F = 7.16, P < 0.001). Separate contrasts demonstrated that OROS MPH was associated with better driving performance than placebo (t = 3.31, P = .001) and se-AMPH ER (t = 2.15, P = 0.03), se-AMPH ER was not associated with better driving than placebo (t = 1.17, P < 0.24)	One AE reported OROS MPH 36 urinary difficulty	No withdrawals but two participants rescheduled due to lack of adherence	McNeil Pediatrics Division of McNeil-PPC, Inc.	
Dopfner 2004 Germany Designed as a non-inferiority trial	Results of repeated measures analysis of variance of SKAMP and PERMP scores, Treatment effect: SKAMP attention: F 2.77 = 27.4, p<0.000 SKAMP deportment: F 2.77 = 18.8; p<0.000 PERMP no. attempted: F 2.77 = 17.8; p<0.000 PERMP no. correct: F 2.77 = 17.2; p<0.000	NR	NR	Medice Arzneimittel Pütter GmbH & Co. KG, Kuhloweg 37, D-58638 Iserlohn	

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Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Efron 1997 Australia (Fair)	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.	Dextroamphetamine 0.15mg/kg Methylphenidate 0.3 mg/kg Both rounded off to the nearest capsule size x 2 weeks then crossover	NR	8.7 years NR NR	ADHD-mixed type=101(81.8%) ADHD-predominantly inattentive=22(17.6%) ADHD-predominantly hyperactive/impulsive=2(1.6%) Mean IQ=98.9	125	NR NR 125

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Efron 1997 Australia (Fair)	% subjects rated by their parents as improved overall compared with their usual selves: 86 (68.8%) vs 90 (72%); p=NS (CTRS-R and CPRS-R data generally corroborated with these proportions of global response to the two stimulants)	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 adverse events: 2(1.6%) vs 2(1.6%)	NR	

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Efron 1998 Australia (Fair)	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.	Dextroamphetamine 0.15mg/kg Methylphenidate 0.3 mg/kg Both rounded off to the nearest capsule size x 2 weeks then crossover	NR	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%)	102	NR NR 102
Elia 1990 US (Fair)	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, school, 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	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	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%)	31	NR NR NR

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Efron 1998 Australia (Fair)	Dextroamphetamine versus methylphenidate: Child's rating: "When I took this medication I felt:" (cases/%) Much worse than usual: 6/5.9 vs 5/4.9 Worse than usual: 13/12.9 vs 8/7.8 About the same as usual: 26/25.7 vs 25/24.5 Better than usual: 23/22.8 vs 35/34.3 Much better than usual: 33/32.7 vs 29/28.4 Child's rating: "How helpful was the medication?" (cases/%) Very helpful: 39/38.6 vs 46/45.1 A bit helpful: 25/24.8 vs 29/28.4 Not sure: 27/26.7 vs 15/14.7 Not very helpful: 5/5 vs 4/3.9 Not at all helpful: 5/5 vs 8/7.8	NR	NR NR	NR	
Elia 1990 US (Fair)	dextroamphetamine=methylphenidate on all measures (limited data provided in graph format) Estimated from graphs (dextroamphetamine vs methylphenidate) <u>Mean changes in (all p=NS):</u> CGI: +2.5 vs +2.8 CPT (# correct): +9 vs +10 CTRS Factor I: -0.4 vs -0.4; CTRS Factor IV: -0.8 vs -0.8 CPRS Factor I: -0.7 vs -0.6; CPRS Factor IV: -1.2 vs -1	NR	NR NR	NR	

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Elia 1991/Schmidt 1994 US (Fair)	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, school, 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).	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	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%)	48	NR NR NR
Elia 1993 US (Fair)	DSM-III criteria for attention deficit disorder with hyperactivity in at least two settings (home, school, 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.	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.	NR	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	33	NR/NR/33

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Elia 1991/Schmidt 1994 US (Fair)	dextroamphetamine=methylphenidate on all measures (limited data provided in graph format) Estimated from graphs (dextroamphetamine vs methylphenidate) <u>Mean changes in (all p=NS):</u> CGI: 2.3 vs 2.4; GAS: 5 vs 6 39-item Conners Factor I (conduct): -0.41 vs -0.41 48-item Conners Factor I (conduct): -0.5 vs -0.39 CPT (# omission errors): -11 vs -11 39-item Conners Factor IV (hyperactivity): -0.9 vs -1 48-item Conners Factor IV (hyperactivity): -1.2 vs -1.0 CPT (# commission errors): -13 vs -14	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	NR	
Elia 1993 US (Fair)	<u>Combined Reading Scores</u> *Percent correct* Dextroamphetamine vs placebo=89.5 vs 86.1; p<0.01 Methylphenidate vs placebo=89.7 vs 86.1; p<0.01 *Mean number of attempts* Dextroamphetamine vs placebo=11.4 vs 9.5; p<0.01 Methylphenidate vs placebo=10.6 vs 9.5; p<0.01 Dextroamphetamine vs methylphenidate: p<0.05 <u>Combined Arithmetic Scores</u> *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	% 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	NR	

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Findling 2006 Australia, Canada, US	Children aged 6–12 years were eligible to participate if they met diagnostic criteria for one of the three subtypes of ADHD as described in the Diagnostic & Statistical Manual of Mental Disorders, 4th Edition and had been on a stable dose of MPH for at least 3 weeks prior to screening. The diagnosis of ADHD was confirmed using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children— Present and Lifetime version (K-SADS-PL). Inclusion Criteria: Male and female children aged 6–12 years (inclusive); On a stable dose of methylphenidate ≥3 weeks prior to screening; diagnosed with ADHD based on DSM-IV criteria for any subtype and confirmed by administration of the K-SADS-PL interview at screening; attending a school setting in which a single teacher could make morning and afternoon assessments of the child's behavior.	Mean Dose: NR MPH-IR twice-daily (morning and lunch-time), EqXL once-daily (morning) followed by placebo at lunch-time, or placebo twice-daily (morning and lunch-time) for 3 weeks. The dosages of the active treatments were determined according to the child's pre-study MPH regimen: Children on a previous total daily dose of 10–20 mg IR MPH or 20 mg ER MPH were randomized to receive either 10 mg MPH-IR twice-daily, 20 mg EqXL once-daily, or placebo; children on a previous total daily dose of 25–40 mg IR MPH or >20 mg to £40 mg ER MPH were randomized to receive 20 mg MPH-IR twice-daily, 40 mg EqXL once-daily, or placebo; and children on a previous total daily dose >40 mg IR MPH or >40 mg ER MPH were randomized to receive 30 mg MPH-IR twice-daily, 60 mg EqXL once-daily or placebo.	NR	Mean age=9.5 yrs (Range=6-12 yrs) 79.2% male 85.8% Caucasian 5.3% Afro-Caribbean 0.3% Asian 1.6% Hispanic 6.9% other	ADHD Subtype: Inattention: 23% Hyperactive/Impulsivity: 5.7% Combined subtype: 71.4%	327 (318 received treatment)	9 withdrawn due to failure to meet all eligibility criteria 318 analyzed

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Findling 2006 Australia, Canada, US	Difference from placebo (95% CI) for MPH-IR vs EqXL Teacher's Ratings: I/O component of 10-item IOWA Conners' Rating Scale 1-week: -2.4 (-3.36, -1.39) vs -1.9 (-2.87, -0.91) 2-week: -2.6 (-3.70, -1.43) vs. -2.4 (-3.58, -1.31) 3-week: -3.4 (-4.53, -2.26) vs. -3.1 (-4.26, -2.00) Teacher's Ratings: O/D component of 10-item IOWA Conners' Rating Scale 1-week: -1.7 (-2.54, -0.38) vs. -1.5 (-2.32, -0.62) 2-week: -1.9 (-2.81, -0.93) vs. -1.8 (-2.69, -0.81) 3-week: -2.4 (-3.36, -1.38) vs. -2.5 (-3.47, -1.48) Parent's Ratings: I/O component of 10-item IOWA Conners' Rating Scale 1-week: -2.3 (-3.31, -1.22) vs. -1.3 (-2.33, -0.23) 2-week: -2.6 (-3.65, -1.53) vs. -1.9 (-2.97, -0.86) 3-week: -3.0 (-4.09, -1.85) vs. -1.7 (-2.78, -0.54) Parent's Ratings: O/D component of 10-item IOWA Conners' Rating Scale 1-week: -2.1 (-3.22, -1.04) vs. -1.8 (-2.89, -0.71) 2-week: -2.5 (-3.64, -1.30) vs. -2.1 (-3.26, -0.92) 3-week: -2.3 (-3.46, -1.16) vs. -1.6 (-2.74, -0.44)	Adverse events occurring in ≥ 3% of patients [placebo (n=46) vs. MPH-IR (n=133) vs. EqXL (n=139)]: Headache: 4.3% vs. 13.5% vs. 18.0% (p=0.059) Anorexia: 0 vs. 3.0% vs. 6.5% (p=0.131) Abdominal pain, upper: 6.5% vs. 6.8% vs. 5.8% (p=0.951) ADHD: 34.8% vs. 4.5% vs. 5.8% (p<0.001) Nasopharyngitis: 6.5% vs. 1.5% vs. 5.8% (p=0.098) Insomnia: 0 vs. 3.8% vs. 4.3% (p-0.497) Decreased appetite: 0 vs. 2.3% vs. 3.6% (p=0.564) Pyrexia: 6.5% vs. 0.8% vs. 2.9% (p=0.077) Vomiting NOS: 4.3% vs. 3.0% vs. 2.2% (p=0.657) Irritability: 2.2% vs. 3.8% vs. 1.4% (p=0.499)	33/318 (10.4%) withdrew before study completion 21/318 (6.6%) withdrew due to adverse events 9/327 post randomization exclusions	Celltech Americas, Inc	

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Findling 2008 US	Patients were aged 6-12 years, who were diagnosed with ADHD according to the DSM-IV-TR. Participants had a Kaufman Brief Intelligence Test IQ score of ≥80, a total score of ≥26 on the ADHD-RS-IV while unmedicated, and normal lab parameters and vital signs. Patients were excluded if they had any comorbid psychiatric diagnosis; a history of seizures during the last 2 years; a tic disorder; or any concurrent illness or skin disorder that might compromise safety or the study assessments.	Methylphenidate Transdermal System (MTS) Initial dose: 10mg/9 hour (range: 10-30mg) Methylphenidate Oral System (MOS) Initial dose: 18mg (range: 18-54mg) Placebo	NR	Mean age: 8.8 years 66.3% males 77.3% Caucasian 14.5% African American 0.7% Asian 7.5% other	ADHD Subtype Combined: 227 (80.5%) Inattentive: 48 (17.0%) Hyperactive/impulsive: 4 (1.4%) Unclassified: 3 (1.1%)	282	113 withdrew total; 8 after randomization but prior to receiving medication; 27 in MTS group vs 25 in MOS group vs 53 in Placebo group 4 lost to follow-up 274 analyzed

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Findling 2008 US	ADHD-RS-IV Total Score (MTS vs MOS vs Placebo) Baseline: 43.0 vs 43.8 vs 41.9 Endpoint: 18.8 vs 21.8 vs 32.1 (p<0.0001 for both interventions vs placebo, no difference between treatment groups) CTRS-R Total Score (MTS vs MOS vs Placebo) Baseline: 34.9 vs 34.9 vs 39.1 Endpoint: 19.4 vs 18.3 vs 31.6 (p<0.0001 for both interventions vs placebo, no difference between treatment groups) CPRS-R at 11am Total Score (MTS vs MOS vs Placebo) Baseline: 52.6 vs 51.2 vs 49.6 Endpoint: 24.6 vs 28.4 vs 37.0 (p=0.0001 for MTS vs Placebo and p=0.0032 for MOS vs Placebo, no difference between treatment groups) CPRS-R at 3pm Total Score (MTS vs MOS vs Placebo) Baseline: 53.7 vs 51.4 vs 49.8 Endpoint: 24.1 vs 29.1 vs 37.7 (p=0.0001 for MTS vs Placebo and p=0.0288 for MOS vs Placebo, no difference between treatment groups)	Most frequently reported AEs (MTS vs MOS vs Placebo) Decreased appetite: 25 vs 17 vs 4 Insomnia: 13 vs 7 vs 4 Nausea: 12 vs 7 vs 2 Vomiting: 10 vs 9 vs 4 Weight decreased: 9 vs 7 vs 0 Tic: 7 vs 1 vs 0 Affect lability: 6 vs 3 vs 0 Nasal congestion: 6 vs 3 vs 1 Anorexia: 5 vs 3 vs 1 Nasopharyngitis: 5 vs 4 vs 2	113 withdrew total; 8 after randomization but prior to receiving medication; 27 in MTS group vs 25 in MOS group vs 53 in Placebo group Withdrawals due to AEs: MTS=7 vs MOS=2 vs Placebo=1	All authors have received grants or research money from multiple pharmaceutical companies	

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Fitzpatrick 1992 (Poor)	Diagnosis of ADD in the Diagnostic Instrument for Childhood and Adolescence (DICA)	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	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	19	NR/NR/NR

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Fitzpatrick 1992 (Poor)	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	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	NIMH Grant MH38118, CIBA-GEIGY provided placebo tablets	

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Gau 2006 Taiwan	Patients, aged 6–15, with a clinical diagnosis of any subtype of ADHD. Patients were included in this study if they were taking MPH on a total daily dose of MPH of 10 mg but not more than 40 mg for past 3 months. They were able to comply with the study visit schedules; and their mothers and teachers were willing and able to complete the weekly assessments.	OROS MPH Mean Dose: 27.7 mg Dose Range: 18-36 mg IR MPH Mean Dose: 26.7 mg Dose Range: 15-30 mg	NR	Mean age=10.5 yrs (Range=6-15 yrs) 90.6% male Ethnicity: NR (study completed in Taiwan)	<u>ADHD diagnosis:</u> Combined: 78.1% Inattentive: 18.8% Hyperactive: 3.1% CTRS-R:S, mean (SD): 72.6 (11.5) CPRS-R:s, mean (SD): 77.6 (9.7) SKAMP, mean (SD): 72.5 (15.5) SAICA, mean (SD): 62.6 (12.5) BSEQ, mean (SD): 24.1 (20.6) <u>Vital signs, mean (SD):</u> Systolic pressure : 97.2 (15.3) Diastolic pressure: 58.2 (10.9) Heart rate: 84.9 (14.8)	64	0/0/64

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Gau 2006 Taiwan	OROS vs IR **CTRS-R, Short Form-C, mean (SD):** <u>Day 13-Baseline:</u> Inattention: -1.38 (2.30) vs. -0.84 (1.97) Hyperactivity-Impulsivity: -3.16 (3.76) vs. -3.22 (4.09) Oppositional: -2.13 (2.97) vs. -1.58 (3.55) ADHD-index: -5.58 (6.38) vs. -5.97 (6.59) <u>Day 27-Baseline, mean (SD) OROS vs IR:</u> Inattention: -1.90 (3.00) vs. -1.44 (2.12) Hyperactivity-Impulsivity: -4.94 (4.11) vs. -4.00 (5.13) Oppositional: -3.03 (3.93) vs. -1.91 (3.90) ADHD-index: -9.20 (7.36) vs. -7.13 (7.62) **CPRS-R, Short Form-C, mean (SD):** <u>Day 13-Baseline:</u> Inattention: -4.78 (5.28) vs. -4.72 (5.31) Hyperactivity-Impulsivity: -6.22 (5.13) vs. -5.25 (5.06) Oppositional: -3.69 (3.36) vs. -3.56 (3.53) ADHD-index: -9.97 (8.26) vs. -9.66 (8.23) <u>Day 27-Baseline:</u> Inattention: -5.63 (5.14) vs. -4.19 (4.84) Hyperactivity-Impulsivity: -7.53 (4.84) vs. -5.84 (5.01) Oppositional: -3.87 (3.32) vs. -3.41 (3.79) ADHD-index: -11.59 (7.82) vs. -9.03 (8.29) **SKAMP, mean (SD):** <u>Day 13-Baseline:</u> Attention: -1.77 (3.16) vs. -1.72 (4.08) Deportment: -2.77 (4.05) vs. -3.25 (4.13) <u>Day 27-Baseline:</u> Attention: -3.71 (3.39) vs. -2.98 (5.29) Deportment: -4.65 (5.53) vs. -4.41 (6.71) At final assessment, OROS group had greater proportion of subjects being very much or much improved than the IR MPH group in CGI rating (84.4% vs. 56.3%, p=0.014)	<u>Percentage of side effects with increased BSEQ score from baseline, day 27, OROS vs. IR MPH:</u> Decreased appetite: 46.9 vs. 59.4 (p=0.316) Insomnia/sleep trouble: 40.6 vs. 46.9 (p=0.614) Stomachache: 31.3 vs. 25.0 (p=0.578) Headache: 21.9 vs. 34.4 (p=0.266) Nightmares: 7.8 vs. 25.0 (0.351) Uninterested in others: 28.1 vs. 40.6 (p=0.292) Irritable: 9.4 vs. 21.9 (p=0.169) Dry mouth: 31.3 vs. 17.2 (p=0.79) Sad/unhappy, prone to crying: 31.3 vs. 43.8 (p=0.302) Anxious: 18.7 vs. 31.3 (p=0.248) Bites fingernails: 18.7 vs. 25.0 (p=0.545) Drowsiness: 7.8 vs. 18.8 (p=0.741) Tics or nervous movements: 7.8 vs. 18.8 (p=0.741) No difference in vital signs on day 28 between groups	0/0	Jansessen-Cilag, Taiwan.	

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Gross 1976 (Poor)	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	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	NR	NR NR NR	NR	50	2 (4%) withdrawn/lost to fu NR/analyzed: dextroamphetamine= 48 vs methylphenidate=46
James 2001 US (Poor)	DSM-IV criteria for combined-type ADHD; ADHD symptoms present in at least two settings	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.	NR	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	35	0/0/35

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Gross 1976 (Poor)	Average improvement: 2.3 vs 2.2; p=NS	Average improvement in average side effects: 0.4 vs 0.5; p=NS	2 (4%) NR	NR	
James 2001 US (Poor)	Adderall vs dextroamphetamine spansules vs immediate release dextroamphetamine vs placebo; differences are insignificant unless otherwise noted CTRS Hyperactivity T score obtained from 9 AM to 12:30 PM: 50.6 vs 53.7 vs 50.5 vs 63.1; DEX IR > DEX span, p<0.025 CPRS Hyperactivity factor score obtained between 1 PM and 3 PM: 2.8 vs 2.3 vs 2.5 vs 3.8; DEX span > ADL, p=0.04 CPS Hyperactivity T score obtained between 4 PM and 7 PM (only available for n=15): 58.6 vs 60.0 vs 60.5 vs 68.0; Dex span > placebo (p=0.007), ADL > placebo (p=0.03), DEX IR = placebo Total attempted math problems: 171.6 vs 187.0 vs 177.4; DEX IR > placebo (p=0.01), DEX span > placebo (p=0.003), ADL = placebo Total correct math problems: 164.6 vs 177.6 vs 167.6 vs 140.2; DEX IR > placebo (p=0.01), DEX span > placebo (p=0.003), ADL=placebo Sleep (hr): 7.6 vs 7.2 vs 7.4 vs 7.8; DEX span and DEX IR decreased sleep > placebo (p<0.001 and p=0.02), ADL=placebo	SERS N#: 3.3 vs 2.9 vs 2.6 vs 2.0 SERS-N sev: 2.7 vs 3.1 vs 2.7 vs 1.8 SERS-P#: 6.3 vs 6.7 vs 6.4 vs 5.9 SERS-P sev: 3.2 3.7 vs 3.2 vs 2.8 Weight (kg): 32.6 vs 32.5 vs 32.7 vs 33.3 Mean magnitude of adverse effects rated by parents (n=20); staff nurse (n=29) for Adderall, immediate-release dextroamphetamine, dextroamphetamine spansules and placebo, uncorrected p-values from ANOVA Trouble sleeping: 3.5 vs 3.0 vs 3.3 vs 2.5, p=0.55; nurses didn't rate Nightmares: 0.6 vs 0.6 vs 0.3 vs 0.3, p=0.24 Stomach aches: 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	0 withdrawals; 0 withdrawals due to adverse events	NR	

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Kauffman 1981 (Fair)	Children diagnosed as "hyperactive," according to a set of predetermined clinical criteria	Dextroamphetamine 10-60 mg Methylphenidate 5-30 mg Placebo Twice daily: morning and noon 6 weeks, then crossover	NR	Mean age NR 100% male 100% white	NR	12	NR/NR/12
Kemner 2005 FOCUS US (Poor)	Children 6 to 12 years of age; meet criteria for a primary diagnosis of ADHD (any subtype) according to the DSM-IV-TR; investigator-rated ADHD-RS score of at least 24 and a Clinical Global Impression-Severity of Illness scale (CGI-S) score of at least 4 ("moderately ill" or worse)	Mean dosages for weeks 1/2/3: Atomoxetine: 32.1 mg/36.8 mg/36.7 mg OROS MPH: 26.8 mg/32.7 mg/32.7 mg (Investigators were allowed to select starting doses and adjust dosages as deemed necessary) Duration: 3 weeks	NR	Mean age=8.9 years 74% male 76.74 white	ADHD subtype Combined: 72% Hyperactive-impulsive: 15% Inattentive: 13% ADHD RS-Investigator-scored (mean): 39.3	1323	NR/NR/NR

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Kauffman 1981 (Fair)	% patients with positive urinalysis: 60 vs 67; p=NS % of patient-weeks with missed doses recorded: 18 vs 13; p=NS	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 between active drugs (p NR) Mean change in height (cm): +0.4 vs +0.4; neither significantly different from placebo	NR NR	Ciba-Geigy Corp.	
Kemner 2005 FOCUS US (Poor)	OROS MPH vs atomoxetine: ADHD RS Total score (mean change in points): -20.24 vs -16; mean difference=4.24 (p<0.001) ADHD-RS responder rates (% pts with 25% or greater reduction in ADHD-RS): 80.2% vs 68.7%; p<0.001 CGI-I responder rates (% pts with scores of 2 or lower): 68.6% vs 52.8%; p<0.001 PSQ mean reductions (points): -9.1 vs -8.7; p<0.001	OROS MPH vs atomoxetine (%) - NS unless otherwise noted: Overall AE incidence: 26.3% vs 28.3% Serious AEs (resulting in prolonged inpatient hospitalization, significant disability or incapacity, onset of life-threatening conditions: 0.8% vs 0.2% Abdominal pain: 0.4 vs 1.1 Abdominal pain, upper: 3.5 vs 4.2 Abnormal behavior: 1.4 vs 1.5 Aggression: 1.2 vs 0.6 Crying: 1.5 vs 0.4 Decreased appetite*: 5.8 vs 3.0 Dizziness: 0.8 vs 1.5 Emotional disturbance: 0.6 vs 1.1 Fatigue*: 0.4 vs 3.0 Headache: 3.9 vs 4.2 Initial insomnia: 1.1 vs 0.2 Insomnia: 6.2 vs 2.3 Irritability: 0.8 vs 1.5 Mood alteration: 1.2 vs 1.3 Nausea*: 1.1 vs 4.9 Somnolence*: 0.9 vs 4.2 Vomiting: 1.3 vs 2.1 *=difference noted in text, but p-value NR	Withdrawals due to adverse events: 4.8% vs 5.5%, p-value NR Overall withdrawals NR	McNeil Consumer and Specialty Pharmaceuticals	

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Kratochvil 2002 US/Canada (Fair)	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)	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	Mean age=10.4 92.5% male 76.7% white	ADHD subtype Combined: 75.9% Hyperactive-impulsive: 1.3% Inattentive: 22.8% ADHD RS-Parent scored (mean): 76.7	228	85 (37.3%) withdrawn/5 (2.2%) lost to fu/218 analyzed (atomoxetine n=178; methylphenidate n=40)

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Kratochvil 2002 US/Canada (Fair)	Atomoxetine vs methylphenidate (mean changes) (p=NS for all) ADHD RS Total score: -19.44 vs -17.78 ADHD RS Hyperactivity/Impulsivity: -9.50 vs -8.48 ADHD RS Inattention subscale: -9.94 vs -9.30 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	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	Eli Lilly	

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Lopez 2003 (Fair)	Children who met ADHD criteria based on the Diagnostic Interview Schedule for Children	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	Mean age=9.0 80.5% male 36% White 27% African American 36% Hispanic	NR	36	0 withdrawn/0 lost to fu/36 analyzed

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

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

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Manos 1999 (Poor)	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	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	NR	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%	159	MPH n=42 (matched by "hand-selecting" by age, diagnostic category and gender to Adderall group), Adderall n=42

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Manos 1999 (Poor)	"Best dose" comparisons of Adderall vs methylphenidate Parent ratings (no significant differences, but p-values NR) ASQ: 49.83 vs 50.64 ARS: 11.79 vs 10.10 Composite ratings: 3.50 vs 3.31 Teacher ratings (no significant differences, but p-values NR) ASQ: 51.47 vs 56.12 SSQ-R, total: 1.67 vs 1.92 SSQ-R, part: 2.23 vs 2.68	Results described as "no differences", but p-values NR Insomnia: 5 (11.9%) vs 2 (4.8%) Decreased appetite: 0 vs 1(2.4%) Tics/nervousness: 0 vs 0	NR NR	NIDA, Maternal and Child Health Program	

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Matochik 1994 US (Fair)	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 major 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	NR	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	37	NR/NR/ 37 analyzed: methylphenidate: n=19 DAMP: n=18

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Matochik 1994 US (Fair)	**Behavioral Effects of methylphenidate vs d-amphetamine** measure; Mean score at end of drug treatment (methylphenidate); 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	1 subject reported adverse events (not specified) within first 2 weeks, and was immediately switched to other drug	None	NR	

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McCracken 2003 US	Potential subjects were screened to meet the following eligibility criteria: age 6 to 12 years; diagnosis of DSM-IV ADHD (combined or hyperactive-impulsive subtype as determined by a comprehensive clinician evaluation and selected modules of the Diagnostic Interview Schedule for Children, Version IV-Lifetime [DISC-IV]) administered by a research staff member with suitable training; no evidence of mental retardation; and history of positive response to psychostimulant medication, or no prior stimulant treatment. Information pertaining to co-occurring psychopathology from the clinical evaluation was supplemented by the Comorbid Disorders Checklist, a parent-report questionnaire composed of DSM-III-R symptom items. All diagnoses were based on DSM-IV criteria.	SLI381 (Adderall XR) 10, 20, or 30mg, placebo, or active control (Adderall 10mg) Mean Dose: NR Subjects who tolerated initial exposure to SLI381 were randomly assigned in crossover design to each of five treatment weeks: SLI381 10mg, SLI381 20mg, SLI381 30mg, Adderall 10mg, and placebo, each administered daily at 7:30 AM	NR	Mean age= 9.5 yrs (SD 1.9) 86.3% male 49% white 15.7% black 23.5% Hispanic 5.9% Asian/Pacific Islander 5.9% other	ADHD diagnosis: Hyperactive-impulsive=2% Combined=98% Duration of prior stimulant treatment: mean=1.7 yrs (SD 1.7) ADHD treatment before study entry: amphetamine only=33.3% methylphenidate only=58.8% none listed=7.8%	51	2 of 51 withdrawn because of withdrawal of consent; 49 randomized for crossover treatment 2 of 47 withdrawn (1 stomachache, 1 developed an exclusion criterion) 45 completed 5 weeks of double-blind portion of study (all treatment conditions) 3 withdrew in extra or "makeup" week ITT=49

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McCracken 2003 US	**p-values for active drug vs placebo:** **Adderall XR 30mg/20mg/10mg/Adderall 10mg** **SKAMP Attention (hours post-dose)** 1.5-hr: 0.0015/0.0513/0.5846/0.0025 4.5-hr: <0.0001/0.0023/0.0269/0.0005 6.0-hr: <0.0001/<0.0001/0.0003/0.0005 7.5-hr: <0.0001/<0.0001/0.0001/0.0002 9.0-hr: 0.0001/0.0072/0.2442/0.8264 10.5-hr: <0.0001/<0.0001/0.0062/0.3250 12.0-hr: 0.0034/0.0077/0.0626/0.3064 **SKAMP Deportment (hours post-dose)** 1.5-hr: 0.0002/0.0031/0.0725/<0.0001 4.5-hr: <0.0001/<0.0001/0.0090/<0.0001 6.0-hr: <0.0001/<0.0001/<0.0001/<0.0001 7.5-hr: <0.0001/<0.0001/0.0083/0.0004 10.5-hr: <0.0001/0.0021/0.0724/0.0246 12.0-hr: 0.0062/0.0531/0.9878/0.7901 **PERMP no. attempted (hours post-dose)** 1.5-hr: 0.0030/0.0283/0.0920/0.0004 4.5-hr: <0.0001/0.0006/0.0136/0.0850 6.0-hr: <0.0001/<0.0001/0.0001/0.0015 7.5-hr: <0.0001/<0.0001/0.0017/0.0157 9.0-hr: <0.0001/0.0001/0.0230/0.0048 10.5-hr: <0.0001/<0.0001/0.0101/0.7626/ 12.0-hr: 0.0017/0.0053/0.9938/0.7508 **PERMP no. correct (hours post-dose)** 1.5-hr: 0.0059/0.0333/0.1121/0.0007 4.5-hr: <0.0001/<0.0001/0.0020/0.0353 6.0-hr: <0.0001/<0.0001/<0.0001/0.0007 7.5-hr: <0.0001/<0.0001/0.0029/0.0667 9.0-hr: <0.0001/<0.0001/0.0128/0.0195 10.5-hr: <0.0001/<0.0001/0.0025/0.3424 12.0-hr: 0.0001/0.0007/0.5420/0.9304	Study medications well tolerated overall. No serious side effects reported or observed. Only anorexia displayed a dose-dependent pattern of increases for Adderall XR doses. Placebo (n=49) vs. Adderall 10mg (n=48) vs. SLI381 10mg(n=48) vs. SLI381 20mg (n=50) vs. SLI381 30mg (n=49) Nervousness: 29 (59.2%) vs. 22 (45.8%), 26 (54.2%) vs. 28 (56.0%) vs. 21 (42.9%) Insomnia: 10 (20.4%) vs. 17 (35.4%) vs. 6 (12.5%) vs. 16 (32.0%) vs. 14 (28.6%) Anxiety: 10 (20.4%) vs. 11 (22.9%) vs. 13 (27.1%) vs. 11 (22%) vs. 9 (18.4%) Emotional lability: 5 (10.2%) vs. 10 (20.8%) vs. 13 (27.1%) vs. 9 (18%) vs. 6 (12.2%) Depression: 5 (10.2%) vs. 4 (8.3%) vs. 5 (10.4%) vs 11 (22.0%) vs. 3 (6.1%) Abdominal pain: 12 (24.5%) vs. 16 (33.3%) vs. 14 (29.2%) vs 18 (36.0%) vs. 17 (34.7%) Headache: 12 (24.5%) vs. 12 (25.0%) vs. 12 (25.0%) vs. 15 (30.0%) vs. 12 (24.5%) Anorexia: 11 (22.4%) vs. 22 (45.8%) vs. 13 (27.1%) vs. 20 (40.0%) vs. 27 (55.1%)	Of the 49 randomized subjects, 3 withdrew due to AE's	Supported by a grant from Shire Pharmaceutical Development Inc.	

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Mikami 2009 US	White adolescents ages 16 to 19 with a primary diagnosis of ADHD, who surpassed clinical cutoffs for ADHD on the ADHD Rating Scale IV and whose parent interview on the Diagnostic Interview Schedule for Children and independent adolescent interview on the Standardized Interview for Adult ADHD supported a diagnosis of ADHD.	A: OROS MPH 72 mg/d B: se-AMPH ER 30 mg/d Dosing schedule: Crossover study, 17 days for each phase (5 days titration period and 12 days on full dose) separated by a 2-week period when participants resumed limited routine medication regimen they were following before the start of the study. On day 10 or 17 of each treatment, patients were given placebo	NR (except during the washout period, where participants resumed regimen they were following before the study, usually methylphenidate or amphetamine on an as-needed or irregular basis, or no treatment)	Age: 17.8 years (SD 1.7) Male: 54% White: 100%	ADHD subtype: Combined: 60% Inattentive: 34% Hyperactive: 6% Medication prior to study: No medication: 5.7% Methylphenidate formulations: 60% Amphetamine formulations: 34.3%	35	NR/NR/35

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Mikami 2009 US	se-AMPH ER vs OROS MPH **Conners-adolescent report, mean (SD):** males: 0.13 (1.03) vs -0.15 (0.87); females: -0.42 (0.81) vs -0.72 (0.67); sex: F(1,32) = 3.98 (p<0.05); medication: F(2,31) = 23.08 (p<0.01); sex x medication: F(2,31) = 0.01; effect size sex x med: η^2 = .00 **HHC-adolescent report, mean (SD):** males: -0.17 (1.06) vs 0.07 (1.27); females: 0.15 (0.88) vs 0.00 (0.74); sex: F(1,30) = 0.05; medication: F(1,30) = 1.96; sex x medication: F(1,30) = 1.83; effect size sex x med: η2 = .05 **HHC-parent report, mean (SD):** males: 0.04 (1.02) vs 0.04 (1.07); females: -0.18 (0.97) vs 0.09 (1.10); sex: F(1,30) = 0.14; medication: F(1,30) = 0.05; sex x medication: F(1,30) = 0.97; effect size sex x med: η2 = .03 **Impaired driving score, mean (SD):** males: 0.07 (3.13) vs -0.69 (1.78); females: 0.24 (2.38) vs -1.48 (1.56); sex: F(1,33) = 0.43; medication: F(2,32) = 5.35 (p<0.01); sex x medication: F(2,32) = 0.28; effect size sex x med: η2 = .01	se-AMPH ER vs OROS MPH **Side effects scale, mean (SD):** males: -0.90 (0.97) vs -0.25 (0.81); females: 0.15 (1.20) vs -0.32 (1.02); sex: F(1,29) = 0.00; medication: F(2,29) = 5.17 (p<0.01); sex x medication: F(2,29) = 1.40; effect size sex x med: η2 = .04	NR	McNeil Consumer and Specialty Pharmaceuticals	

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Muniz 2008 US	Patients were 6-12 years with ADHD according to the DSM-IV-TR, who had been stabilized on a total daily dose or the nearest equivalent dose of 40 to 60 mg of *d,l*-MPH or 20 to 30 mg *d*-MPH for at least 2 weeks prior to screening. Children were excluded if they had a tic disorder or Tourette's syndrome, history of seizures, psychiatric illness or substance abuse disorder, taking prohibited concomitant medications or ADHD medication other than methylphenidate, taking antidepressant or psychotropic medications, had begun psychotherapy within 3 months prior to randomization or who were home schooled.	*d*-MPH-ER 20-30mg/day *d,l*-MPH-ER 36-54mg/day Placebo	NR	Mean age: 9.5 years 65.5% male 42.9% Caucasian 27.4% Black 28.6% Hispanic 1.2% other	DSM-IV ADHD diagnosis Inattentive type: 9 (10.7%) Combined type: 75 (89.3%)	84	3 withdrew 0 lost to fu 84 analyzed

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Muniz 2008 US	d-MPH 20mg/day vs d,l-MPH 36mg/day; d-MPH 30mg/day vs d,l-MPH 54mg/day SKAMP-Combined score change from pre-dose to 2-hours post-dose -10.65 vs -5.94 (p<0.001); -11.17 vs -7.52 (p=0.001) d-MPH 20mg vs Placebo: p<0.05; d-MPH 30mg vs Placebo: p<0.001 d,l-MPH 36mg and d,l-MPH 54 mg vs Placebo: p<0.001 SKAMP-Attention score change from pre-dose d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.001 at 1 and 3 hours; p<0.05 at 2 and 6 hours d,l-MPH 36 mg/day vs d-MPH 20mg/day: p<0.05 at 10 hours; p<0.001 at 11 and 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day: p<0.001at 1 and 3 hours; p<0.05 at 2, 4, and 6 hours d,l-MPH 54mg/day vs d-MPH 30mg/day: p<0.05 at 11 and 12 hours SKAMP-Deportment score change from pre-dose d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.001 at 1, 2, 3, and 4 hours d,l-MPH 36mg/day vs d-MPH 20mg/day: p<0.1 at 10, 11 and 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day: p=0.019 at 0.5 hours; p<0.001 at 1 and 2 hours; p<0.05 at 3 and 4 hours d,l-MPH 54mg/day vs d-MPH 30mg/day: p<0.05 at 11 and 12 hours Change in number of attempted math problems d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.05 at 1 and 3 hours d,l-MPH 36mg/day vs d-MPH 20mg/day: p=0.01 at 11 hours; p=0.001 at 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day: p<0.05 at 1, 3, and 4 hours Change in number of accurate math problems d-MPH 20mg/day vs d,l-MPH 36mg/day: p<0.05 at 1, 2, and 3 hours d,l-MPH 36mg/day vs d-MPH 20mg/day: p<0.05 at 11 and 12 hours d-MPH 30mg/day vs d,l-MPH 54mg/day: p<0.05 at 1, 2, 3, and 4 hours d,l-MPH 54mg/day vs d-MPH 30mg/day: p<0.05 at 11 and 12 hours	*d*-MPH 20mg/day vs *d*-MPH 30mg/day vs *d,l*-MPH 54mg/day vs *d,l*-MPH 36mg/day vs Placebo Total: 8 vs 15 vs 5 vs 12 vs 3 Headache: 4 vs 6 vs 2 vs 5 vs 0 Nausea: 1 vs 1 vs 1 vs 0 vs 0 Nasal congestion: 1 vs 1 vs 0 vs 1 vs 0 Decreased appetite: 0 vs 1 vs 1 vs 1 vs 0 Vomiting: 0 vs 1 vs 1 vs 0 vs 0 Skin laceration: 0 vs 1 vs 0 vs 1 vs 0 Somnolence: 1 vs 1 vs 0 vs 0 vs 0 Insomnia: 0 vs 1 vs 0 vs 1 vs 0 Abdominal pain upper: 1 vs 1 vs 0 vs 0 vs 0 Abdominal pain: 0 vs 1 vs 0 vs 1 vs 0	3 withdrew consent, none withdrew due to AEs	All authors have received grants or research money from multiple pharmaceutical companies	

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Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Newcorn 2008 US	Patients aged 6-16 years, who met DSM-IV criteria for ADHD, any subtype, symptom severity was ≥1.5 SD above the US age and gender norms as assessed by the ADHD-RS-IV - Parent version. Patients were excluded if they had seizures, bipolar disorder, a psychotic illness, or a pervasive development disorder or who were taking concomitant psychoactive medications; and those with anxiety and tic disorders.	Atomoxetine 0.8-1.8 mg/kg per day (administered as divided twice-daily dose) - mean final dose was 1.45 mg/kg per day or 53mg/day Osmotically released methylphenidate 18-54 mg/day (administered as a single morning dose) - mean final dose was 39.9 mg/day or 1.16 mg/kg per day for patients <12 years and 41.7 mg/day or 0.88 mg/kg per day for patients ≥12 years Placebo	NR	Mean age: Atomoxetine=10.3 years; Methylphenidate= 10.2; Placebo=10.1 74.2% male Ethnicity: NR	ADHD Subtype Hyperactive/impulsive: 2% Inattentive: 28% Combined: 70%	516	93 withdrew from acute phase; 42 withdrew from crossover phase 16 lost to follow up from acute phase; no lost to follow up in crossover phase 516 analyzed in acute phase; 178 analyzed in crossover phase

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Newcorn 2008 US	Atomoxetine vs MPH vs placebo (mean change) ADHD-RS total score: -14.4 vs -16.9 vs -7.3 (p=0.003 for Atomoxetine vs Placebo; p<0.001 for MPH vs Placebo; p=0.02 for Atomoxetine vs MPH) ADHD-RS total score for prior stimulant users: -12.4 vs -15.1 vs -6.2 (p=0.02 for MPH vs placebo; p=0.03 for MPH vs atomoxetine) ADHD-RS total score for those naïve to stimulants: -17.9 vs -19.7 vs -9.0 (p=0.004 for atomoxetine vs placebo; p<0.001 for MPH vs placebo) ADHD-RS inattentive subscale: -7.3 vs -9.0 vs -4.1 (p=0.006 for MPH vs atomoxetine) ADHD-RS inattentive subscale for prior stimulant users: -5.9 vs -7.8 vs -3.3 (p=0.02 for MPH vs atomoxetine) ADHD-RS inattentive subscale for those naive to stimulants: -9.7 vs -11.0 vs -5.2 ADHD-RS impulsivity/hyperactivity subscale: -7.1 vs -7.9 vs -3.2 ADHD-RS impulsivity/hyperactivity subscale for prior stimulant users: -6.5 vs -7.3 vs -2.8 ADHD-RS impulsivity/hyperactivity subscale for those naive to stimulants: -8.2 vs -8.7 vs -3.8 CGI ADHD severity index: -1.2 vs -1.5 vs -0.7 CGI ADHD severity index for prior stimulant users: -0.9 vs -1.3 vs -0.6 CGI ADHD severity index for those naive to stimulants: -1.5 vs -1.8 vs -0.8 CPRS ADHD Index: -7.8 vs -10.2 vs -2.3 CPRSADHD Index for prior stimulant users: -5.9 vs -8.2 vs -1.1 CPRS ADHD Index for those naive to stimulants: -10.9 vs -13.5 vs -3.9 Daily Parent Ratings of Evening and Morning Behavior - Revised; Morning: -0.31 vs -0.25 vs 0.61 Daily Parent Ratings of Evening and Morning Behavior - Revised; Evening: -0.48 vs -0.53 vs 0.60 CHQ psychosocial summary score: 11.9 vs 12.7 vs 12.0 CHQ psychosocial summary score for prior stimulant users: 11.4 vs 13.1 vs 12.1 CHQ psychosocial summary score for those naive to stimulants: 9.9 vs 9.8 vs 12.0 **After Crossover: Response to either treatment arm** 60 of 178 (34%) responded to either atomoxetine or MPH, but not both 78 of 178 (44%) responded to both treatments 40 of 178 (22%) did not respond to either treatment Of 70 patients who did not respond to MPH in the acute phase, 30 (43%) subsequently responded to atomoxetine Of 69 patients who did not respond to atomoxetine in the crossover phase, 29 (42%) had previously responded to MPH	Atomoxetine vs methylphenidate vs placebo Any: 149 (67%) vs 146 (67%) vs 40 (54%) Headache: 39 (18%) vs 25 (11%) vs 7 (10%) Decreased appetite: 31 (14%) vs 37 (17%) vs 2 (3%) Pain in upper abdomen: 24 (11%) vs 22 (10%) vs 4 (5%) Any report of insomnia: 15 (7%) vs 29 (13%) vs 1 (1%) Irritability: 14 (6%) vs 13 (6%) vs 1 (1%) Nausea: 9 (4%) vs 13 (6%) vs 6 (8%) Insomnia: 9 (4%) vs 17 (8%) vs 1 (1%) Vomiting not otherwise specified: 15 (7%) vs 8 (4%) vs 4 (5%) Somnolence: 14 (6%) vs 4 (2%) vs 3 (4%) Cough: 7 (3%) vs 8 (4%) vs 4 (5%) Fatigue: 12 (5%) vs 5 (2%) vs 1 (1%) Initial insomnia: 6 (3%) vs 12 (6%) vs 0 (0%)	93 withdrew from acute phase; 12 for AEs 42 withdrew from crossover phase; 3 for AEs	Eli Lilly	

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Palumbo 2008/Daviss 2008 US (Fair)	Children ages 7 to 12 years of any race and ethnic background who were in school, and met DSM-IV criteria for ADHD of any subtype.	A: Clonidine (mean end-of-study dose 0.24±0.11 mg/d) B: Methylphenidate (mean end-of-study dose 30.2±18.9 mg/d) C: Combination: Clonidine (0.23±0.13 mg/d) + Methylphenidate (25.4±18.2 mg/d) D: Placebo (not reported on in this evidence table) for 16 weeks -- an 8-week dose titration period (4 weeks for clonidine, then 4 weeks for methylphenidate) and an 8-week maintenance dose period.	NR	Age: 9.5 years (SD 1.6) Male: 80.3% White: 77.9% Black: 10.7% Hispanic: 6.6% Other: 4.9%	Pubertal: 6.5% Family history: ADHD: 37.7% Tics: 4.1% Treatment history: Stimulant: 46.7% Clonidine: 6.6% Comorbid ODD: 47.1% Comorbid conduct disorder: 9.2%	122	44/6/NR

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Palumbo 2008/Daviss 2008 US (Fair)	Clonidine vs Methylphenidate vs Combination Conners ASQ-Teacher, mean (SD) changes from baseline to week 16: -3.35 (5.78) vs -5.07 (6.79) vs -7.28 (7.91) Treatment Effects on the Conners ASQ-Teacher: Methylphenidate vs. no methylphenidate: -2.9; 95% CI, -5.1 to -0.8; P=0.008 Clonidine vs. no clonidine: -1.4; 95% CI, -3.6 to 0.7; P=0.19 Methylphenidate x Clonidine interaction: P=0.69 Methylphenidate vs Clonidine: -1.5; 95% CI, -4.6 to 1.6; P=0.34 Combination vs Methylphenidate: -1.9; 95% CI, -4.9 to 1.2; P=0.23 Combination vs Clonidine: -3.4; 95% CI, -6.4 to -0.4; P=0.03 Treatment Effects on the Conners ASQ-Parent: Methylphenidate vs. no methylphenidate: -1.2; 95% CI, -3.7 to 1.2; P=0.31 Clonidine vs. no clonidine: -3.7; 95% CI, -6.1 to -1.3; P=0.003 Methylphenidate x Clonidine interaction: P=0.56 Methylphenidate vs Clonidine: 2.5; 95% CI, -1.0 to 5.9; P=0.16 Combination vs Methylphenidate: -3.0; 95% CI, -6.4 to 0.4; P=0.08 Treatment Effects on the CGAS: Methylphenidate vs. no methylphenidate: 3.7; 95% CI, -0.2 to 7.5; P=0.06 Clonidine vs. no clonidine: 7.5; 95% CI, 3.6 to 11.4; P=0.0002 Methylphenidate x Clonidine interaction: P=0.02 Methylphenidate vs Clonidine: -3.6; 95% CI, -9.0 to 1.8; P=0.18 Combination vs Methylphenidate: 2.7; 95% CI, -2.6 to 8.1; P=0.32 Combination vs Clonidine: -0.9; 95% CI, -6.2 to 4.4; P=0.73	Methylphenidate vs Clonidine vs Combination One subject receiving combination therapy (0.2 mg/d of clonidine and 5 mg/d of methylphenidate) was withdrawn at week 14 after experiencing a prolonged QTc interval (>440 ms) as well as ECG findings suggestive of left ventricular hypertrophy. This child had a normal echocardiogram and never reported physical complaints suggestive of cardiovascular problems. A second subject taking methylphenidate 20 mg/d was withdrawn in the last week of the double-blind phase complaining of repeated incidences of tachycardia and heart palpitations. No abnormalities were observed in this subject's vital signs or ECGs. Severe AEs: 10 events (3 subjects) vs 30 events (10 subjects) vs 39 events (9 subjects) Weight, mean change (SD) in kg: 0.3 (2.3) vs 2.0 (2.9) vs 0.6 (2.3); taking Methylphenidate P=0.0007 Abnormal ECG rate, QTc >120 ms: 3.5% vs 6.5% vs 0.0% **AEs rated at least moderate on AEs log (occurring ≥5% within one or more treatment groups):** Any AE: 58.6% vs 83.9% vs 75.0%; P=0.0006 Nervousness: 17.2% vs 32.3% vs 31.3%; P=0.04 Somnolence: 6.9% vs 41.9% vs 34.4%; P<0.0001 Apathy: 13.8% vs 32.3% vs 18.8% Depression: 17.2% vs 22.6% vs 12.5% Dyspepsia: 24.1% vs 19.4% vs 15.6% Insomnia: 3.4% vs 16.1% vs 12.5% Fatigue: 0.0% vs 22.6% vs 15.6%; P=0.03 Headache: 3.4% vs 16.1% vs 15.6%	Clonidine vs Methylphenidate vs Combination Total withdrawals: 5 (16%) vs 11 (38%) vs 8 (25%); four of the withdrawals in the Methylphenidate group occurred during the first 4 weeks (i.e., before actually receiving methylphenidate -- see intervention column). Due to AE as the primary reason for withdrawal: 1 (3.2%) vs 1 (3.4%) vs 3 (9.4%) Due to AE, not necessarily as the primary reason for withdrawal: 2 (6.9%) vs 1 (3.4%) vs 5 (15.6%)	NINDS grant 5R01 NS039087. Additional NIH support came from K23 MH065375 and K24 AA000301.	Dosing schedule: Clonidine: Initiated with half of a 0.1-mg scored tablet at bedtime, and increased by half of a tablet every 3 days. Dose titration continued until either the optimal dose or the max dose of 0.6 mg/d was reached. Methylphenidate: Started with a 5-mg immediate-release capsule before school. Daily dose allowed to increase by 5 mg every 3 days. Doses were adjusted to optimal effect (max dose 60 mg/d).

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Palumbo 2008/Daviss 2008 US (Fair) (continued)		**Moderate or Severe Adverse Events on Pittsburgh Side Effect Rating Scale** Parent Ratings: Worried/anxious: 3.4% vs 16.1% vs 0.0%; Methylphenidate effect P=0.03 Dull/tired/listless: 6.9% vs 58.1% vs 37.5%; Clonidine effect P<0.0001 Headache: 6.9% vs 19.4% vs 6.3% Stomachache: 10.3% vs 25.8% vs 12.5% Crabby/irritable: 31.0% vs 35.5% vs 31.3% Tearful/sad/depressed: 13.8% vs 19.4% vs 12.5% Socially withdrawn: 6.9% vs 16.1% vs 6.3% Trouble sleeping: 20.7% vs 16.1% vs 12.5% Loss of appetite: 13.8% vs 29.0% vs 9.4% Dizzy/lightheaded: 3.4% vs 6.5% vs 3.1% Dry mouth: 0.0% vs 16.1% vs 6.3%; Clonidine effect P=0.01 Palpitations: 3.4% vs 0.0% vs 0.0% Chest pain: 6.9% vs 0.0% vs 0.0% Sedation/drowsiness: 0.0% vs 54.8% vs 28.1%; Clonidine effect P<0.0001; Methylphenidate effect P=0.08 Teacher Ratings: Worried/anxious: 6.9% vs 12.9% vs 6.3% Dull/tired/listless: 6.9% vs 58.1% vs 31.3%; Clonidine effect P<0.0001 Headache: 6.9% vs 6.5% vs 6.3% Stomachache: 0.0% vs 6.5% vs 3.1% Crabby/irritable: 0.0% vs 12.9% vs 15.6% Tearful/sad/depressed: 6.9% vs 6.5% vs 9.4% Socially withdrawn: 13.8% vs 16.1% vs 15.6% Trouble sleeping: 3.4% vs 9.7% vs 0.0% Loss of appetite: 0.0% vs 3.2% vs 0.0% Dizzy/lightheaded: 0.0% vs 0.0% vs 6.3% Dry mouth: 0.0% vs 0.0% vs 0.0% Palpitations: 0.0% vs 0.0% vs 0.0% Chest pain: 3.4% vs 0.0% vs 0.0% Sedation/drowsiness: 0.0% vs 41.9% vs 21.9%; Clonidine effect P<0.0001			

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Pelham 1987 (Poor)	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	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	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	13	NR/NR/NR

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Pelham 1987 (Poor)	Methylphenidate vs sustained release methylphenidate, t-test, p-value: Daily frequencies Following rules: 3.5 vs 4.3, t=1.8, p=NS Noncompliance: 3.4 vs 4.3, t=-2.5, p<0.05 Positive peer behaviors=100.2 vs 95.8, t=0.8, p=NS Conduct problems: 0.3 vs 0.4, t=-0.4, p=NS Negative verbalizations=3.4 vs 4.8, t=-2.3, p<0.05 N. of time outs/day: 0.5 vs 0.7, t=-1.2, p=NS Classroom % on task=95.2 vs 96.5, t=-0.6, p=NS % on following rules=93.9 vs 92.2, t=0.6, p=NS Timed math No. attempted=21.0 vs 21.7, t=-0.5, p=NS % correct=9.3 4 vs 94.4, t=-0.5, p=NS Timed reading No. attempted=19.8 vs 18.2, t=1.4, p=NS % correct=79.8 vs 77.9, t=0.4, p=NS Seatwork % completion=86.1 vs 89.1, t=-0.9, p=NS % correct=83.7 vs 82.9, t=0.3, p=NS Teacher rating: 1.9 vs 3.4, t=-1.3, p=NS Counselor rating: 106.4 vs 105.9, t=0.1, p=NS Positive daily report card (% of days received): 83.2 vs 81.8, t=0.2, p=NS Observed interactions Positive peer: 97.9 vs 95.2, t=1.6, p=NS Negative peer: 1.4 vs 1.5, t=-0.2, p=NS No interactions: 0.7 vs 3.3, t=-1.8, p=NS	Evidence of anorexia: Standard methylphenidate=4 (30.8%) vs 5 (38.5%); p=NS	NR NR	NR	

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Pelham 1990 (Poor)	Diagnosis of ADHD based on structured parental interview and parent and teacher rating scales (not specified)	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	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	22	NR/NR/NR

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Pelham 1990 (Poor)	Placebo vs Methylphenidate vs sustained release methylphenidate vs pemoline vs sustained release dextroamphetamine, ALL results significant compared to PLACEBO unless otherwise noted (p=NS): Daily frequency measures: % following activity rules: 75.2 vs 80.9 vs 78.1 vs 79.0 vs 81.0 Noncompliance: 5.5 vs 2.3 vs 2.3 vs 2.0 vs 1.7 Positive peer interactions: 82.8 vs 92.6 (p=NS) vs 104.5 vs 111.1 vs 100.0 Conduct problems: 0.73 vs 0.25 (p=NS) vs 0.18 vs 0.18 vs 0.21 Negative verbalizations: 5.4 vs 1.6 vs 2.0 (p=NS) vs 1.6 vs 1.4 Classroom measures: % following rules: 85 vs 92 (p=NS) vs 94 vs 95 vs 95 Timed reading # attempted: 14.3 vs 18 vs 16.4 vs 15.7 vs 17.5 % correct: 69 vs 73 vs 73 vs 75 vs 74 Seatwork % completed: 70 vs 78 vs 77 vs 79 (p=NS) vs 76 % correct: 84 vs 84 vs 87 (p=NS) vs 87 vs 86 Teacher rating (ACTRS): 3.8 vs 2.3 vs 2.3 vs 1.5 vs 1.7 Counselor rating (ACTRS): 6.3 vs 4.8 vs 5.0 vs 5.1 vs 4.5 Positive daily report (% days rec'd): 51 vs 63 (p=NS) vs 64 vs 71 vs 67	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/Muscle 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	NR	

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Pelham 1999a (Fair)	DSM-IV diagnosis of ADHD	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	Concurrent behavioral point system	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 ODD 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	21	NR/NR/NR

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Pelham 1999a (Fair)	Adderall q AM vs MPH bid vs MPH q AM b = p<0.05 vs MPH bid; c = p<0.05 vs MPH q AM <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	% children rated by Counselor/Parent/Teacher as displaying side effects at a moderate-severe leve on at least one day: MPH q AM vs MPH 0.3/0.3/0.15 vs MPH 0.3/0.3/0.3 vs Adderall q AM 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	Shire	

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Pelham 1999b (Fair)	DSM-IV diagnosis of ADHD	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	NR	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	25	NR/NR/NR

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Pelham 1999b (Fair)	Adderall 7.5/12.5 vs Methylphenidate 10 mg/17.5 mg; results of ANOVA of methylphenidate vs Adderall; p-value: Classroom variables Rule-following Seatwork: 89.7/90.7 vs 84.3/87.8, 4.06, p=NS Peer tutoring: 95.1/95.0 vs 91.4/94.8, 3.71, p=NS Computer: 91.1/94.4 vs 87.3/92.6, 2.80, p=NS Seatwork completion: 71.6/67.1 vs 69.5/69.2, 0.00, p=NS Seatwork accuracy: 87.6/87.3 vs 87.9/87.1, 0.00, p=NS Observational measures On-task behavior: 89.0/89.9 vs 89.2/89.6, 0.00, p=NS Disruptive behavior: 6.4/6.4 vs 6.9/6.2, 0.15; p=NS Daily report card: 83.8/82.8 vs 76.4/81.7, 6.63, p<0.05 Recess rule violations: 1.0/0.4 vs 1.3/0.7, 3.21, p=NS Counselor ratings I/O: 2.4/2.2 vs 3.4/2.6, 1.4, p<0.001; O/D: 1.0/0.8 vs 2.3/1.1, 13.85, p<0.01 Teacher ratings I/O: 1.2/1.2 vs 1.8/1.1, 0.72, p=NS; O/D: 0.7/0.4 vs 1.3/0.6, 3.22, p=NS 5:00-6:00 parent ratings I/O: 0.9/0.5 vs 1.5/1.0, 5.25, p<0.05; O/D: 0.8/0.6 vs 1.2/1.1, 4.09, p=NS All evening parent ratings I/O: 1.5/1.4 vs 2.6/1.7, 3.33, p=NS; O/D: 1.9/1.2 vs 2.4/1.2, 12.17, p<0.01 Point system measures Following rules: 75.4/79.9 vs 71.4/74.5, 10.38, p=NS Attention: 68.2/68.2 vs 64.0/64.3, 5.47, p=NS Noncompliance: 0.9/1.2 vs 2.2/0.8, 5.65; p=NS Interruption: 6.2/6.8 vs 10.6/6.7, 7.48, p=0.025 Complaining/whining: 2.9/2.0 vs 4.1/2.6, 4.12, p=NS Positive peer behaviors: 8.1/7.8 vs 8.8/8.8, 1.82, p=NS Conduct problems: 0.4/0.2 vs 1.4/0.1, 5.17, p=NS Negative verbalizations: 2.0/2.2 vs 6.1/2.2, 7.89, p=0.01	% children rated by Counselor/Parent as displaying 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	Shire	

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Pelham 2001 (Fair)	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	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	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	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 Teacher IOWA Conners ratings Inattention/overactivity=9.65 Oppositional/defiant=4.07 Teacher abbreviated Conners rating=14.96 Teacher peer relations rating=5.33	70	2 (2.8%) withdrawn/lost to fu NR/analyzed 68 5 children missed one of 3 testing sessions

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

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Pelham 2011 US (Fair)	Boys (girls were eligible but none enrolled) ages of 7-9 years with ADHD, an estimated full-scale IQ of at least 80, and who were receiving a stable dose of IR MPH before enrollment.	A: MTS 20 cm2 worn for 24 hours B: IR MPH 10 mg tid C: Placebo for 3 weeks (within-subject, random crossover design)	NR	Age: 8.6 years (SD 1.1) Male: 100% White: 50% Black: 20% Native American: 10% Other: 20%	IQ score: 95.3 (SD 9.9) Combined subtype of ADHD: 80% Inattentive subtype of ADHD: 20% Patients also meeting criteria for ODD or CD: 80%	10	1/0/9

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Pelham 2011 US (Fair)	Placebo vs MTS vs MPH tid Rule violations, mean (SD): 81.3 (62.1) vs 40.4 (52.4; MTS vs placebo F(1,8)=9.96, P=0.01) vs 45.3 (41.3; MPH tid vs placebo F(1,8)=15.59, P<0.01); MTS vs MPH tid F(1,8)=0.35, P=NS Math correct, mean (SD): 21.6 (25.0) vs 29.6 (22.7; MTS vs placebo F(1,8)=5.14; P=0.05) vs 34.3 (29.7; MPH tid vs placebo F(1,8)=30.86, P<0.001); MTS vs MPH tid F(1,8)=1.12, P=NS Inattention/overactivity teacher rating: 9.7 (5.1) vs 5.8 (4.9; MTS vs placebo F(1,8)=8.83, P=0.02) vs 6.0 (4.3; MPH tid vs placebo F(1,8)=8.50, P=0.0195); MTS vs MPH tid F(1,8)=0.02, P=NS Oppositional–defiant teacher rating: 9.0 (5.0) vs 4.8 (5.3; MTS vs placebo F(1,8)=9.18, P=0.02) vs 4.7 (4.3; MPH tid vs placebo F(1,8)=12.24, P<0.01); MTS vs MPH tid F(1,8)=0.00, P=NS	NR by treatment group Parent-reported appetite reduction: 33% on IR MPH or MTS vs 22% on placebo There was only one case of emotional lability reported which occurred during MTS usage. Five events were recorded as moderate in severity, one for IR MPH (malaise), none for MTS, and four in the placebo condition (vomiting, stomach ache, faintness, and flu-like symptoms).	Placebo vs MTS vs MPH tid Total withdrawals: 1 (10%) vs 0 vs 0 Due to AE: 0 vs 0 vs 0	Noven Pharmaceuticals	The doses of IR MPH and MTS were deemed to be equivalent based on data from the development of the MTS (33 mg/24 hr for MTS vs. 30 mg/24 hr for IR MPH).

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Pliszka 2000/Faraone 2001 (Fair)	DISC criteria for ADHD; ≥ 1.5 SD above the mean for his/her age and sex on the IOWA CTRS Inattention/Overactivity (I/O) factor; parent Conners Global Index score similarly elevated	Adderall < 60 kg = 5-15 mg > 60 kg = 10-30 mg 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	NR	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	58	5 (8.6%) withdrawn/0 lost to fu/58 analyzed Adderall n=20 Methylphenidate n=20 Placebo n=18

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Pliszka 2000/Faraone 2001 (Fair)	Adderall vs methylphenidate IOWA CTRS I/O: AM: 0.44 vs 0.78; p=NS PM: 0.54 vs 0.85, p=NS Average: 0.49 vs 0.81, p<0.05 IOWA CTRS A/D AM: 0.25 vs 0.47, p=NS PM: 0.33 vs 0.51, p=NS Average: 0.29 vs 0.49, p<0.05 Conners Global Index: 1.04 vs 1.28, p=NS CGI Improvement: 1.6 vs 2.35, p<0.05 Responders %: 90 vs 65 Final weight (kg): 37 vs 33.2, p=NS Dosing regimen: 70% of Adderall subjects required only an AM dose vs 85% in the methylphenidate group received 2 or more doses per day; p=0.003	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	Shire	

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Prasad 2007	Patients were children and adolescents who met DSM-IV criteria for ADHD by clinical investigator assessment and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children-Present and Lifetime Versions (K-SADS-PL). Children were 7–15 years of age, and were not intellectually impaired in the viewpoints of the investigators. They were required to have a symptom severity score ≥ 1.5 standard deviations above the investigator-rated ADHD-Rating Scale-IV (ADHD-RS) age norm for their ADHD subtype to be eligible for enrolment. Patients were assessed for other psychiatric disorders by clinical assessment and by the K-SADS-PL (disruptive behaviors, anxiety, and affective disorders modules).	Atomoxetine: Mean Dose: 1.5 mg/kg/day. commenced on 0.5 mg/kg/day. After a minimum of 7 days, patients who, in the judgment of the investigator, had clinically significant residual symptoms and who were tolerating atomoxetine, could have a dose increase to approximately 1.2 mg/kg/day. After a minimum of two further weeks, a dose increase to a maximum of 1.8 mg/kg/day was permitted, if required, based on the investigator's assessment of clinical response (efficacy and tolerability) SCT: Mean daily dose of single therapy short acting MPH was 0.80 mg/kg/day, and for long-acting OROS MPH was 1.03 mg/kg/day. SCT was defined as any intervention regarded by the investigator/treating physician that would benefit the patient, and that they would use as appropriate in their standard clinical practice, including the option of no therapy. SCT could include any combination of medicines (apart from atomoxetine) and/or simple behavioral counseling approaches	NR	Mean age: 10.9 yrs (SD 2.2) (Range: 6.9-15.9 yrs) 88.6% male 99% Caucasian	Atomoxetine vs SCT Previously treated with stimulants: 59.6% vs 70.1%, p=0.140 patients that have not previously taken any medication: 27.96% vs 19.6%, p=0.187 Pts that have taken medications other than stimulants: 13 pts vs 10 pts, p=0.663 <u>ADHD subtype:</u> Combined: 181(90.5%), p=0.055 Hyperactive: 4(2%), p= >0.999 Inattentive: 15(7.5%), p=0.030 <u>Other disorders in >5% patients:</u> Oppositional defiant disorder: 124(61.7%), p=0.563 Conduct disorder: 14(7%), p= >0.999	201	7 withdrew in study period I, 26 in atomoxetine group withdrew in study period II, 6 SCT pts withdrew in study period II,

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Prasad 2007	No differential treatment effect between SCT and atomoxetine. LS mean ± SE of the total score of the CHIP-CE increased to 38.4± 1.3 for atomoxetine and to 30.8±1.3 for the SCT group patients treated with atomoxetine was superior in health compared with SCT patients. Atomoxetine patients was just greater than one SD below the US norm of 50. Overall treatment effect for atomoxetine was significant (p<0.001) No significant difference in reduction of FBIM total score between atomoxetine vs SCT Improved investigator-rated ADHD-RS score was higher for atomoxetine pts at wk 10 (p<0.001)	Atomoxetine vs SCT headache: 22(21.2%) vs 8(8.2%), p=0.016 Nausea: 18 (17.3%) vs 3(3.1%), p= <0.001 Weight decreased: 8 (7.7%) vs 8(8,2%), p= >0.999 Decreased appetite: 8(7.7%) vs 6(6.2%), p=0.784 Vomiting: 9(8.7%) vs 2(2.1%), p=0.059 Abdominal pain upper: 7(6.7%) vs 3(3.1%), p=0.334 Cough: 6(5.8%) vs 4(4.1%), p=0.749	Total withdrawals depends on the phase of the study; 6 withdrawals due to adverse events	Eli Lilly	

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Sangal 2006 US	Patients were 6 to 14 years old at study entry. They were diagnosed with ADHD using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria as well as severity criteria. Diagnosis was assessed by the investigator's clinical evaluation and by the administration of several modules of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version structured interview. In addition, patients had an ADHD Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHD RS) score at least 1.0 standard deviation above normative values for age and sex for either the inattentive or hyperactive/impulsive subscore, or for the combined score. All patients scored at least 80 on the Wechsler Intelligence Scale for Children -3rd edition.	Atomoxetine Mean final dose: 58.27 mg/day (range = 15-100), or 1.56mglkg per day Methylphenidate: Mean final dose was 42.29 mg/day (range = 15-60), or 1.12 mg/kg per day	NR	Mean age: 10.1 yrs (SD 2.0) 75.3% male 72.9% Caucasian	ADHD Subtype: Hyperactive/Impulsive: 2.4% Inattentive: 29.8% Combined: 67.9% Present Comorbid Conditions: ODD: 48.2% Conduct Disorder: 3.5% Anxiety Agoraphobia: 1.2% Prior stimulant exposure: 56.5%	85	6 withdrew after 1st acute treatment phase; 4 withdrew after 2nd acute treatment phase 50 analyzed (25 excluded from analysis) n=79 for safety

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Sangal 2006 US	Actigraphic Sleep Measures Change from Baseline (SD) Atomoxetine vs. Methylphenidate; [95% CI] Sleep-onset latency, min: 12.06 (27.07) vs. 39.24 (40.77); p<0.001 [-12.82, -6.49] Total nap time, min: 4.49 (10.41) vs. 3.04 (7.92); p=0.475 [-1.68, 3.55] Total sleep interval, min: -15.00 (45.10) vs. -35.89 (56.10); p=0.004 [6.81, 34.15] Assumed sleep time, min: -15.26 (44.25) vs. 29.61 (53.00); p=0.016 [2.73, 25.73] Interrupted sleep time, min: 0.26 (15.04) vs. -6.28 (17.48); p=0.025 [0.80, 11.69] Sleep interruptions, no.: -1.31 (6.83) vs. -4.36 (6.33); p=0.011 [0.70, 5.19]	TEAs occurring in at least 10% of the 79 patients in either treatment group (Atomoxetine vs. Methylphenidate) Decreased appetite: 11.4% vs. 24.1% (p=0.30) Headache: 19.0% vs. 15.2% (p=0.698) Insomnia: 6.3% vs. 26.6% (p<0.001) Appetite decreased: 11.4% vs. 15.2% (p=0.357) Irritability: 11.4% vs. 15.2% (p=0.263) Pharyngitis: 15.2% vs. 8.9% (p=0.173) Cough: 12.7% vs. 8.9% (p=0.625) Somnolence: 15.2% vs. 3.8% (p=0.057) Abdominal pain, upper: 11.4% vs. 5.1% (p=0.248) Fatigue: 11.4% vs. 3.8% (p=0.121)	No withdrawals due to adverse events; total withdrawals depends on which phase of the study	Sponsored by Eli Lilly; data were analyzed by statisticians at Eli Lilly.	

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Schachar 2008 Canada	Patients were aged 6-15 years with a diagnosis of ADHD according to the DSM-IV, with an IQ of ≥85 on the Wechsler Intelligence Scales for Children within the previous 12 months, must be mentally and physically competent to give consent. Patients were excluded if they were allergic to MPH or amphetamines or had a history of serious adverse reactions to MPH or had a lack of response to MPH; if they had serious or unstable medical illness, co-morbid psychiatric illness of sufficient severity to require treatment, or currently receiving psychotropic medications or herbal treatments; and if they had disorders of the sensory organs, autism, psychosis, or any unstable psychiatric conditions.	MPH 1.2mg/kg per day (average daily dose=31.2mg/day; range: 20-60mg/day) Multi-layer release was given as a single morning dose, with placebo at lunch-time (MLR MPH) Immediate release was given as two equal doses at morning and lunch-time (IR MPH) Placebo was given at both morning and lunch-time (Placebo)	NR	Mean age: 11.3 years 88% male Ethnicity: NR	NR	18	1 withdrew, none were lost to follow-up 17 analyzed

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Schachar 2008 Canada	Placebo vs IR MPH vs MLR MPH (mean) Stop task - go task (msec): 721.8 vs 670.9 vs 673.1 Stop task - mean delay (msec): 349.6 vs 409.3 vs 426.1 Stop task - stop signal reaction time (msec): 372.2 vs 261.6 vs 247.1 Continuous performance test - errors of omission (n): 60 vs 31 vs 47.7 Continuous performance test - errors of commission (n): 24.1 vs 25.6 vs 24.5 Arithmetic test - number completed: 22.9 vs 26 vs 20.5 Arithmetic test - number correct: 17.6 vs 20.7 vs 20.5 Arithmetic test - percent correct: 75.8% vs 77.5% vs 81.2% IOWA-C - overall change from baseline: 2.03 vs -0.66 vs -1.38 IOWA-C - Inattention/overactivity subscale change from baseline: 3.20 vs -0.98 vs -1.26 IOWA-C - Aggression/defiance subscale change from baseline: 0.86 vs -0.33 vs -1.5 Problem situations change from baseline: 1.49 vs -0.35 vs -0.47 Communicative pragmatics change from baseline: 2.91 vs -0.27 vs -0.89 CGI of "much improved" or "very much improved": 17.6% vs 58.8% vs 76.5%	MLR MPH vs IR MPH vs Placebo Headache: 1 vs 1 vs 1 Tremor: 0 vs 1 vs 1 Somnolence: 1 vs 1 vs 0 Asthenia: 1 vs 0 vs 0 Psychosis: 0 vs 0 vs 1 Anorexia: 0 vs 1 vs 0 Rhinitis: 0 vs 1 vs 0 Infection: 0 vs 0 vs 1 Pruritus: 0 vs 1 vs 0	1 withdrew, none due to AEs	Some authors are employed by or receive money from Purdue Pharma, but study was not sponsored by Purdue Pharma	

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Sharp 1999 (Fair)	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	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	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)	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	32	1 (3.1%) withdrawn/lost to fu NR/analyzed=32

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Sharp 1999 (Fair)	% patients with CGI--GI ratings of "very much improved" or "much improved": 85% vs 83%; p=NS	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	NR	Meta-analysis of this 100% female trial

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Silva 2005 US	Eligible participants were children 6–12 years of age who met DSM-IV (C-DISC-4 1997) criteria for a primary diagnosis of ADHD and whose parents provided written consent for their participation in the study. Assent to participate was also obtained from all children. Inclusion criteria required that children were treated and stabilized on a total daily dose of 20–40 mg MPH for at least 2 weeks prior to enrollment. Female participants were required to be premenarchal, sexually abstinent, or using an approved method of contraception; those of childbearing potential were required to have a negative urine pregnancy test prior to enrollment.	single doses of extended-release MPH (ER-MPH) 20 and 40 mg, modified-release MPH (OROS-MPH) 18 and 36 mg, and placebo Mean Dose: NR	NR	Mean age: 9.4 yrs (SD 1.9) 63% male 63% Caucasian 14.8% African American 0% Asian 22.2% other	ADHD subtype Inattentive: 27.8% Hyperactive/impulsive: 1.9% Combined inattentive/hyperactive: 70.4%	54	1 withdrew

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Silva 2005 US	Mean (SD) Postdose Scores (ER-MPH 20mg/ER-MPH 40mg/OROS-MPH 18mg/OROS-MPH 36mg/placebo) SKAMP-Attention (hours postdose) 0.5-hr: 1.70 (0.73)/1.78 (0.94)/1.97 (0.97)/1.79 (0.93)/1.86 (1.03) 1.0-hr: 1.37 (1.04)/1.37 (1.03)/1.70 (1.07)/1.76 (1.13)/2.26 (1.17) 2.0-hr: 1.08 (0.78)/0.89 (0.81)/1.31 (0.97)/1.63 (1.10)/1.79 (1.17) 3.0-hr: 1.30 (0.85)/1.01 (0.80)/1.50 (1.01)/1.65 (1.16)/2.08 (1.03) 4.0-hr: 1.31 (0.81)/1.28 (0.88)/1.57 (1.02)/1.49 (0.86)/1.95 (1.00) 6.0-hr: 1.47 (0.85)/1.21 (0.98)/1.55 (0.94)/1.60 (0.99)/2.09 (0.93) 8.0-hr: 1.75 (0.84)/1.41 (1.01)/1.64 (1.04)/1.62 (0.97)/2.18 (1.07) 10.0-hr: 1.84 (0.93)/1.74 (1.04)/1.56 (0.91)/1.81 (1.14)/2.20 (1.10) 12.0-hr: 2.13 (0.98)/1.89 (0.83)/1/73 (1.09)/1.53 (1.06)/2.22 (0.98) SKAMP-Deportment (hours postdose) 0.5-hr: 1.37 (1.29)/1.19 (1.16)/1.48 (1.21)/1.46 (1.38)/1.74 (1.49) 1.0-hr: 1.12 (1.17)/0.79 (1.08)/1.39 (1.31)/1.33 (1.42)/2.10 (1.52) 2.0-hr: 0.91 (0.95)/0.48 (0.65)/1.07 (1.12)/1.19 (1.30)/2.06 (1.46) 3.0-hr: 0.96 (0.93)/0.58 (0.74)/1.27 (1.15)/1.09 (1.10)/2.15 (1.52) 4.0-hr: 1.12 (1.05)/0.63 (0.77)/1.36 (1.24)/1.12 (1.13)/2.19 (1.41) 6.0-hr: 1.20 (1.02)/0.70 (0.83)/1.37 (1.13)/1.16 (1.25)/2.14 (1.24) 8.0-hr: 1.36 (1.29)/0.92 (1.04)/1.35 (1.09)/1.39 (1.33)/2.00 (1.30) 10.0-hr: 1.65 (1.23)/1.25 (1.18)/1.40 (1.28)/1.27 (1.24)/2.06 (0.98) 12.0-hr: 1.94 (1.21)/1.54 (1.19)/1.54 (1.25)/1.33 (1.17)/2.14 (1.29) SKAMP-Combined (hours postdose) 0.5-hr: 1.52 (0.89)/1.46 (0.94)/1.70 (0.95)/1.61 (1.03)/1.79 (1.17) 1.0-hr: 1.24 (0.96)/1.04 (0.95)/1.53 (1.08)1.53 (1.17)/2.18 (1.21) 2.0-hr: 0.99 (0.71)/0.67 (0.58)/1,18 (0.93)/1.40 (1.11)/1.94 (1.18) 3.0-hr: 1.12 (0.74)/0.78 (0.67)/1.37 (0.98)/1.35 (0.98)/2.12 (1.14) 4.0-hr: 1.21 (0.82)/0.93 (0.74)/1.46 (1.04)/1.29 (0.91)/2.08 (1.08) 6.0-hr: 1.32 (0.82)/0.93 (0.82)/1.46 (0.92)/1.37 (1.01)/2.12 (0.96) 8.0-hr: 1.54 (0.98)/1.15 (0.94)/1.48 (0.94)/1.49 (1.04)/2.08 (1.05) 10.0-hr: 1.74 (1.02)/1.48 (1.01)/1.47 (0.96)/1.52 (1.06)/2.13 (0.90) 12.0-hr: 2.03 (1.00)/1.67 (0.92)/1.63 (0.96)/1.42 (1.02)/2.17 (0.96)	Small number of AE's (18) were reported. Total AE's (ER-MPH 20mg/ER-MPH 40 mg/OROS-MPH 18 mg/OROS-MPH 36 mg/placebo: 3.7%/5.6%/9.4%/11.3%/3.8% Headache: 3.7%/1.9%/1.9%/5.7%/1.9%	1 post-randomization exclusion 53/54 completed study receiving all 5 treatment conditions according to protocol	Novartis Pharmaceuticals Corporation	

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Simpson 1980 US (Fair)	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 disorders, CNS infection, genetic syndromes, metabolic disorders, or other medical conditions incongruous with developmental hyperactivity.	MPH, D-amphetamine, placebo for 8 weeks each	NR	Age 6-12, mean age NR 100% male Ethnicity NR	NR	12	NR/NR/12

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Simpson 1980 US (Fair)	Results reported only for each individual child, post-hoc analysis reported to indicate that *where a positive effect was seen*, dextroamphetamine was superior to methylphenidate - but these data are not presented.	NR	0 withdrawals; 0 withdrawals due to adverse events	NR	

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Sonuga-Barke, 2009 Companion to Swanson 2004 COMACS Study	See Swanson 2004	See Swanson 2004	See Swanson 2004	See Swanson 2004	See Swanson 2004	See Swanson 2004	See Swanson 2004

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Sonuga-Barke, 2009 Companion to Swanson 2004 COMACS Study	See Swanson 2004	Barkley Stimulant Side Effect Rating Scale Effect of dose on the sleep/appetite factor scores: F[2,174]=5.12; P=0.007. The dose effect for the other factor scores (emotionality, disengaged, dizzy, uninterested, and aches) were NS. No overall effect of formulation (F[1,172]=0.01; p=0.972). Sleep problems/poor appetite were significantly worse overall on active drug vs placebo ($t^{Concerta}$ [175]=5.17; P<0.001; $t^{Equasym\ XL/Metadate\ CD}$ [173]=3.41; P=0.001). In the emotion domain, symptoms of anxiety and tearfulness improved significantly on active drug as opposed to placebo ($t^{Concerta}$ [175]=2.31; P=0.022; $t^{Equasym\ XL/Metadate\ CD}$ [173]=3.18; P=0.002). The treatment effects for the other factors were NS. The interaction between formulation and AE factor was not significant although there was trend in this direction (F[5,806]=2.83; P=0.095). Concerta vs Equasym XL/Metadate CD vs Placebo Absolute levels of AEs (cut-off score of ≥4): Insomnia and trouble sleeping: 32.37% vs 30.64% vs 21.97% Decreased appetite: 37.57% vs 31.79% vs 19.65% Irritable: 31.40% vs 30.23% vs 44.77%; P=0.001 Sad/unhappy: 16.96% vs 14.04% vs 12.87% Prone to cry: 19.08% vs 14.45% vs 21.97% Anxious: 21.39% vs 19.08% vs 34.68%; P<0.001	See Swanson 2004	See Swanson 2004	

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Spencer 2011 US (Fair)	Adult outpatients with ADHD between 19 and 60 years, meeting ADHD DSM IV diagnostic criteria, receiving stable dose of IR methylphenidate for at least 4 weeks, demonstrating clinical response CGI-I of much or very much improved, were tolerant of the efficacious dose (score on the tolerability index of 0 or 1) and were satisfied with their treatment response (score of 1 or 2 on treatment satisfaction rating scale). Normal blood pressure SBP<40mmHg and DBP<90mmHg for a period of 4 weeks on a stable dose of IR Methylphenidate TID.	A. OROS Methylphenidate Mean (SD): 57.2 (26.4) B. IR Methylphenidate TID Mean (SD): 73.8 (25.2) Max dose 1.3mg/Kg/d or 144mg/d Time period: 6 weeks	NR	Mean age: 36.3 years Male:49% Ethnicity: NR	GAF score: 65.4 ADHD AISRS score: 10.8 ADHD CGI-I Very much improved: 75% Much improved: 25% Satisfaction scale Completely satisfied: 37.7% Mostly satisfied: 60.4%	53	28/0/53
Starr 2005 US Subanalysis of FOCUS	See Kemner 2005; African American group only	Mean dosages: 32.5 mg vs 1.1 mg/kg/day	See Kemner 2005	Mean age=8.8 years 82% male 100% African American	ADHD subtype Hyperactive-impulsive: 14.1% Inattentive: 9.1% Combined: 14.7% Family history of ADHD: 47% Prior treatment for ADHD: 52% Duration of ADHD: 27 months Baseline ADHD-RS: 40.6 Baseline CGI-SI: 4.9	183	NR/NR/NR

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Spencer 2011 US (Fair)	Methylphenidate IR TID vs MPH OROS (p-values are between groups) Change from baseline in ADHD AISRS rating scale (from graph): -5.2 vs-1.2, p=0.7, $F_{(1, 52)}$=0.1 % of patients satisfied with treatment(completely and mostly): 100% vs 68.3%, x^2=4.7, p=0.2 Proportion of patients who had complete compliance: 17% vs 46%, x^2=3.4, p=0.7 Mean(SD) no. of missed doses: 7.3 (6.8) vs 3.3 (4.2), F(1,51)=6.3, p=0.02 Mean change from baseline in SBP: 0.9 vs 1.7, p=0.9 Mean change from baseline in DBP: -1.5 vs 1.1, p=0.3 Mean change from baseline in pulse: 2.8 vs 4.9, p=0.1 Outliers analysis of cardiovascular data, p value between Methylphenidate IR vs OROS. SBP>140mmHg15% vs 13%, p=0.8 DBP>90mmHg8% vs 2%, p=0.3 pulse>90bpm 31% vs 30%, p=0.9	Methylphenidate IR TID vs MPH OROS (p-values are between groups) CGI Tolerability index: x^2=1.4, p=0.7 Proportion of patients reporting no adverse events: 58% vs 44% Proportion of patients reporting no interference of drug with patient functioning: 42% vs 49% Proportion of patients reporting significant interference: 0% vs 5% Proportion of patients where AE outweighed benefit: 0% vs 3%	Methylphenidate IR TID vs MPH OROS Total withdrawal: 8% vs 19.5% Withdrawals due to AE: NR vs NR	McNeil Pediatrics	
Starr 2005 US Subanalysis of FOCUS	OROS MPH vs atomoxetine: ADHD RS Total score (mean change in points): Week 1: -9.8 vs -7.5, NS Week 2: -14.5 vs -11.4; NS Week 3: -20.4 vs -15.9; p<0.03 ADHD-RS responder rates ≥ 30% reductions (% pts): 77.4% vs 61.1%; p<0.03 ≥ 50% reductions (% pts): 58.3% vs 35.2%: p<0.006 CGI-I responder rates (% pts with scores ≤2): 68.4% vs 49.1%; p<0.01 PSQ total scores: 19.8 vs 23.4; p<0.009 % parents stating that their child was doing "better than" or "somewhat better than" before treatment: 85.1% vs 63.8%; p-value NR	Treatment-related adverse events: 19.2% vs 19% Upper abdominal pain: 4.8% vs 1.7% Decreased appetite: 4% vs 1.7% Headache: 4.0% vs 1.7% Insomnia: 3.2% vs 0 Nausea: 0.8% vs 3.4% Somnolence: 0.8% vs 5.2% Sedation: 0 vs 5.2% p-values NR	Withdrawals due to adverse events: 0.8% vs 1.7%; p-value NR Overall withdrawals NR	McNeil Consumer & Specialty Pharmaceuticals	

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Steele 2006 Canada	Physically healthy, male and female outpatients, aged 6 - 12 years inclusive, with a documented Diagnostic Statistical Manual-Fourth Edition (DSM-IV) diagnosis of Attention-Deficit/Hyperactivity Disorder. These criteria were confirmed by a clinical and structured interview (the Kiddie-Schedule for Affective Disorders and Schizophrenia -Present and Lifetime Version, K-SADS-PL, version 1.0). Subjects were medication naïve or currently on ADHD medication therapy; had a baseline Clinical Global Impression-Severity (CGI-S) score of 4 or greater (at least "moderate" severity); and had to demonstrate significant after-school/evening behavioral difficulties as assessed by the clinician via parent/child interviews. To approximate clinical practice settings, psychotropic medications to treat non-ADHD disorders and psychological interventions were permitted as long as the treatment/intervention had been stable for a minimum of 4 weeks prior to entry and did not change nor newly commence during the trial.	OROS-MPH: Mean Dose: 37.8 mg/day (SD 11.9) Initiated on 18 mg once daily. Over 4 weeks, the subjects were titrated by weekly increases, at the investigators' discretion; to the next dose level (27 mg, then 36 mg) to a maximum of 54 mg. IR-MPH: Mean Dose: 33.3 mg/day (SD 13.2) Initiated at whatever dose the clinician felt was appropriate. Over 4 weeks each individual dose was titrated weekly by 5 mg or 10 mg increments, according to the manufacturer's recommendations and the investigator's clinical judgment, to a suggested maximum daily dose of 60 mg.	Psychotropic medications to treat non-ADHD disorders and psychological interventions permitted as long as treatment/intervention had been stable at least 4 weeks prior to entry and did not change nor newly commence during the trial	Mean age=9.1 yrs (Range=6-12 yrs) 83.4% male 86.9% Caucasian 3.4% black 9% other	ADHD diagnosis: predominantly inattentive=18.6% combined type=79.3% predominantly H/I=2.1%	147	2 withdrawn (didn't receive study medication) ITT n=143 Safety analysis n=145

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Steele 2006 Canada	Achieved remission (SNAP-IV-18) at endpoint: 44% vs. 16%; p=0.0002 Remission rates higher in OROS-MPH group than in IR-MHP group at week 4 (33% vs, 14%; p=0.01) and at week 8 (47% vs. 16%; p=0.0003) <u>Mean change from baseline score (SD) at study endpoint (OROS-MPH vs. IR-MPH):</u> SNAP-IV 26-item (ADHD + ODD items) Scale: -25.5 (18.7) vs. -17.5 (15.2) SNAP-IV 18-item (ADHD items) Scale: -19.6 (13.9) vs. -14.3 (11.6) IOWA Conners Parent Rating Scale, Total: -9.4 (8.5) vs. -6.0 (5.9) IOWA Conners Parent Rating Scale, Inattention/Overactivity Sub-scale: -5.4 (4.5) vs. -3.9 (3.2) Conners Parent Rating Scale: -27.5 (21.9) vs. -19.2 (15.6) Parent Stress Index, Short Form: +14.0 (19.2) vs. +6.1 (14.8) Visual analog scale (mm): homework: -31.8 (29.6) vs. -23.0 (33.8) Visual analog scale (mm): social play: -17.9 (30.4) vs. -7.5 (27.0) CGI-I: mean rating (SD): 2.0 (1.2) vs. 2.6 (1.4); p=0.0008 CGI-S: mean change from baseline rating (SD): -2.2 (1.2) vs. -1.6 (1.4); p=0.0005 Parent satisfaction with current ADHD medication: mean rating (SD): 4.0 (1.3) vs. 3.4 (1.3); p=0.003	Adverse events were reported for 82% of subjects in both groups. No serious adverse events were reported. Any event: 82% vs. 82% Any possibly medication related event: 64% vs. 52% Decreased appetite: 24% vs. 32% Headache: 19% vs. 16% Insomnia: 17% vs. 14% Abdominal pain: 14% vs. 12% Nervousness: 13% vs. 12% Emotional lability: 13% vs. 3% Agitation: 11% vs. 7% Fatigue: 10% vs. 3% Flu-like symptoms: 10% vs. 10% Sleep disorder: 4% vs. 10%	Total =24 (16.6%) AEs=8 (5.5%)	Janssen-Ortho Inc., Canada	

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Stephens 1984 US (Poor)	DSM-III diagnosis of attention-deficit disorder with hyperactivity	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	Mean age=8.8 86.1% male Race NR	ACRS mean score=17.9	31	NR/NR/NR
Swanson 2003	Unclear, no details provided	Unclear, no details provided	Unclear; no information provided about baseline characteristics	Yes	Yes for community-school teacher and parent ratings; unclear for laboratory teacher ratings	Yes, double-blind, double-dummy	Yes, double-blind, double-dummy

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Stephens 1984 US (Poor)	Pemoline vs methylphenidate (p=NS for all comparisons) Mean number of total errors: Paired associates learning Learning: 37.80 vs 38.64 Retention: 20.67 vs 20.58 Spelling Learning: 27.33 vs 26.19 Retention: 14.39 vs 16.42	NR	NR NR	NR	
Swanson 2003	Unclear; for primary outcome -N included in analysis NR. N's for secondary outcome are reported.	N/A	Unclear	N/A	N/A

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Swanson 2004/Sonuga-Burke 2004 COMACS Study US	Children 6-12 years old with diagnoses of a DSM-IV subtype of ADHD (inattentive type, hyperactive-impulsive type, or combined type) who were being treated with methylphenidate (MPH) 10 to 60 mg/d. Children were deemed otherwise healthy by medical history, physical examination, vital sigh measurements, and by clinical laboratory assessments. Children also had to demonstrated the ability to swallow PLA study-treatment capsules whole and without difficulty.	Methylphenidate extended release (Metadate CD®) vs methylphenidate extended release (Concerta®) vs placebo Dose level assigned according to preexisting MPH dose requirements: Low (≤ 20 mg): 20 mg vs 18 mg Medium (> 20 to 40 mg): 40 mg vs 36 mg High (> 40 mg): 60 mg vs 54 mg Duration 7 days	NR	9.6 years 73.8% male 68.9% white 11.5% black 1.7% Asian 12.4% Hispanic 5.4% other	Subtype of ADHD Inattentive: 13% Hyperactive/Inattentive: 4.8% Combined: 82.1%	184	27 (14.7%) withdrawn/lost to fu NR/184 analyzed (Metadate n=174; Concerta n=181; placebo n=183)
Taylor 2000 US (Fair)	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.	NR	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	22	1 withdrawn 0 lost to fu; 21 analyzed, all exposed to both DAMP & modafinil

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Swanson 2004/Sonuga-Burke 2004 COMACS Study US	Effect sizes: Metadate CD® vs Concerta® SKAMP deportment Hours post-dose 0.0: -.23 vs -.18 1.5: 0.82 vs 0.52 3.0: 0.89 vs 0.50 4.5: 0.80 vs 0.50 6.0: 0.76 vs 0.66 7.5: 0.54 vs 0.51 12: 0.06 vs 0.25 SKAMP attention 0.0: -0.59 vs -0.58 1.5: 0.70 vs 0.41 3.0: 0.72 vs 0.48 4.5: 0.66 vs 0.42 6.0: 0.65 vs 0.64 7.5: 0.50 vs 0.53 12: 0.06 vs 0.25 PERMP - # correct math problems 0.0: -0.27 vs -0.33 1.5: 0.57 vs 0.42 3.0: 0.56 vs 0.42 4.5: 0.59 vs 0.40 6.0: 0.58 vs 0.54 7.5: 0.50 vs 0.53 12: 0.10 vs 0.28	Parent ratings of side effects on the Barkley Scale: no differences (data NR) Metadate CD® vs Concerta® vs placebo Gastrointestinal disorders: 4.6% vs 6.1% vs 7.1% Abdominal pain upper: 3.4% vs 4.4% vs 3.3% Vomiting NOS: 0.6% vs 0.6% vs 2.2% Infections and infestations: 0.6% vs 2.8% vs 1.1% Injury, poisonings, and procedural complications: 3.4% vs 1.7% vs 2.7% Metabolism and nutrition disorders: 4.6% vs 6.1% vs 2.2% Anorexia: 2.9% vs 2.8% vs 1.1% Appetite decreased NOS: 1.7% vs 3.3% vs 0.5% Nervous system disorders: 3.4% vs 5.5% vs 5.5% Headache NOS: 1.7% vs 3.9% vs 3.3% Psychiatric disorders: 6.9% vs 7.2% vs 9.3% Insomnia: 1.7% vs 1.7% vs 3.3% Irritability: 1.7% vs 1.1% vs 2.7%	Total withdrawals: NR Withdrawals due to adverse events: 0 vs 0.5% vs 1%	Celltech	
Taylor 2000 US (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	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	NR	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.

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Taylor 2001 US (Fair)	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.	A: DAMP maximum 20 mg/day, mean 10.2 mg/day B: Guanfacine maximum 2.0 mg/day, mean 1.10 mg/day C: Placebo 2-week treatment phases of placebo, guanfacine, and dextroamphetamine (DAMP) were separated by 4-day washouts 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.	NR	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.	17	0/0/17

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Taylor 2001 US (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	Muscle tension 5 (29.4%) on DAMP Fatigue 4 (23.5%) on guanfacine	0 withdrawals	NR	Data from the first phase was not reported separately. Outcomes were presented as combined data from all phases for each drug. The authors examined the effect of sequence in the crossover design, and report that no effect or interactions were found.

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Tourette's Syndrome Study Group 2002 (Fair)	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	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,	Nonpharmacologic (e.g., behavioral) interventions were allowed, but remained unchanged throughout the course of the study	Mean age=10.2 85.4% male 88.3% white	100% had Tourette's syndrome Other psychiatric diagnoses: OCD: 15.8% ODD: 38.1% Conduct disorder: 9% GAD: 9.2% MDD: 5% 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% Classroom observations On-task behavior: 76.7% Disruptive behavior: 10.9%	136	19/0/136
van der Meere 1999 The Netherlands (Fair)	Children, age range 7 to 12 years, all diagnosed with ADHD (DSM-III-R)	Methylphenidate 0.6 mg/kg Clonidine 4.0 mg/kg (using 25 mg Dixarit dragees) 7 weeks Twice daily dosing: Methylphenidate=breakfast/lunch; Clonidine=breakfast/evening	NR	Mean age=9.2 86.8% male Ethnicity NR	6 (11.3%) Conduct Disorder 14 (26.4%) Oppositional Defiant Disorder 2 (3.8%) Depressive/Anxiety Disorder Mean Full Scale IQ=90	53	NR/NR/53

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Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Tourette's Syndrome Study Group 2002 (Fair)	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	Clonidine vs methylphenidate Sedation (% patients): 48% vs 14%; p=0.004 Sedation (% patients rated as moderate or severe): 35% vs 8%; p=0.007	Total Withdrawals MPH=4(10.8%) Clonidine=4 (11.8%) Combination=4 (12.1%) Placebo=7 (21.9%) Withdrawals due to adverse events Combination=1 (3.4%) for ECG change; no other withdrawals due to adverse events in other groups	NR	
van der Meere 1999 The Netherlands (Fair)	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	NR	NR NR	Sophia Foundation for Medical Research and Boehringer Ingelheim BV, the Netherlands	

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Wang 2007 China, Korea and Mexico	Patients aged 6-16 years weighing between 20 and 60 kg, who met DSM-IV criteria for ADHD, had a severity of ≥25 for boys and ≥22 for girls, or >12 for a specific subtype, on the ADHD-RS-IV- Parent Version: INV, as well as the CGI-ADHD-S. Patients were excluded if they had a history of bipolar, psychotic or pervasive development disorders; suicidal risk; ongoing use of psychoactive medications other than the study drug; those with motor tics, a diagnosis or family history of Tourette's syndrome or those who met DSM-IV criteria for anxiety disorder.	Atomoxetine Initial dose: 0.8mg/kg per day (once daily in morning) Range: 0.8-1.8mg/kg per day Methylphenidate (MPH) Initial dose: 0.2mg/kg per day (twice daily in morning and at lunch) Range: 0.2-0.6mg/kg per day	Limited OTC use	Mean age: 9.7 years 83% male 91.5% East/Southeast Asian 8.5% Hispanic	DSM-IV subtype Combined: 196 (59.4%) Inattentive: 124 (37.6%) Hyperactive/Impulsive: 10 (3%) Previous exposure to stimulants: 80 (24.2%)	330	40 withdrew 330 analyzed for safety 326 analyzed for efficacy
Weiss 2007 Canada	Patients aged 6-17 years with DSM-IV diagnosis of ADHD, with an intelligence quotient of ≥80 on the WISC-III within the previous 12 months, score of ≥1.5 SD from norm on the Conners' ADHD index. Patients were excluded if they were allergic to MPH or amphetamines or had ah history of serous adverse reactions to MPH or had a lack of response to MPH; had a serious or unstable medical illness, co-morbid psychiatric illness of sufficient severity to require treatment, or currently receiving psychotropic medications or herbal treatments; history of drug abuse, alcohol abuse, disorder of the sensory organs, autism, psychosis, or any unstable psychiatric conditions.	MLR MPH (administered once daily) IR MPH (administered twice daily) Initial dose: 10mg for ≤20kg, 20mg for 20-35kg, 30mg for >35kg up to 40mg for ≤20kg, 50mg for 20-35kg, 60mg for <35kg	NR	Mean age: 11.0 years 82% male 83% White 6% Black 4% Asian 7% other	MPH naïve: 59%	90	11 withdrew 1 lost to follow-up 90 analyzed

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Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wang 2007 China, Korea and Mexico	Atomoxetine vs MPH Completion rate: 84.1% vs 91.6% (p=0.044) Response rate: 77.4% vs 81.5% (p=0.404) ADHD-RS-IV Parent:Inv total mean change from baseline: -21.1 vs -21.6 ADHD-RS-IV Parent:Inv inattentive subscale mean change from baseline: -11.3 vs -12.0 ADHD-RS-IV Parent:Inv hyperactivity/impulsivity subscale mean change from baseline: -9.7 vs -9.5 CPRS-R:S ADHD index mean change from baseline: -11.1 vs -11.0 CPRS-R:S Cognitive problems/inattention mean change from baseline: -5.8 vs -6.0 CPRS-R:S Hyperactivity mean change from baseline: -5.9 vs -4.9 CPRS-R:S Oppositional mean change from baseline: -3.0 vs -3.4 CGI-ADHD-S mean change from baseline: -2.3 vs -2.5	Atomoxetine vs MPH Anorexia: 61 (37.2%) vs 42 (25.3%) p=0.024 Decreased appetite: 46 (28.0%) vs 32 (19.3%) Nausea: 33 (20.1%) vs 17 (10.2%) p=0.014 Somnolence: 43 (26.2%) vs 6 (3.6%) p<0.001 Headache: 25 (15.2%) vs 16 (9.6%) Dizziness: 25 (15.2%) vs 12 (7.2%) p=0.024 Abdominal pain: 15 (9.1%) vs 15 (9.0%) Pyrexia: 11 (6.7%) vs 17 (10.2%) Vomiting: 19 (11.6%) vs 6 (3.6%) p=0.007 Cough: 11 (6.7%) vs 10 (6.0%) Upper respiratory tract infection: 9 (5.5%) vs 11 (6.6%) Fatigue: 13 (7.9%) vs 5 (3.0%) Irritability: 7 (4.3%) vs 10 (6.0%) Rhinorrhea: 7 (4.3%) vs 10 (6.0%) Insomnia: 5 (3.0%) vs 9 (5.4%)	40 withdrew 24 withdrew due to AEs (18 in Atomoxetine group vs 6 in MPH group)	NR, but corresponding author is from Eli Lilly	
Weiss 2007 Canada	MLR MPH vs IR MPH (mean questionnaire results at end of double-blind phase) CGI - therapeutic effect-investigator: 2.8 vs 2.9 CGI - adverse events-investigator: 1.6 vs 1.7 CGI - global improvement-investigator: 2.3 vs 2.3 CGI - global improvement-parent: 2.5 vs 2.6 CGI - global improvement-teacher: 2.4 vs 2.4 CPRS - ADHD index: 56.6 vs 56.8 CPRS - Cognitive/inattention: 56.7 vs 56.3 CPRS - hyperactivity: 56.9 vs 57.2 CPRS - Oppositional: 56.9 vs 56.8 CTRS - ADHD index: 56.3 vs 52.8 CTRS - Cognitive/inattention:51.8 vs 51.1 CTRS - hyperactivity: 55.4 vs 52.0 CTRS - Oppositional: 53.5 vs 51.5	MLR MPH vs IR MPH Anorexia: 20% vs 24.4% Insomnia: 20% vs 16.7% Nervousness: 17.8% vs 17.8% Headache: 13.3% vs 12.2% Somnolence: 8.9% vs 4.4% Abdominal pain: 6.7% vs 8.9% Depression: 6.7% vs 4.4% Emotional liability: 3.3% vs 6.7%	11 withdrew 4 withdrew due to AEs	Purdue Pharma	

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Whitehouse 1980 US (Fair)	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	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	NR	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)	34	4 (11.8%) withdrawn/0 lost to fu/30 analyzed

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Whitehouse 1980 US (Fair)	Mean change scores (visit 3 compared to visit 1) for sustained release vs standard: <u>Teacher</u> Total score: -1 vs -8, p<0.05 Conduct Problem: 0 vs -3, p<0.05 Inattentive/Passive: 0 vs 0 Tension/Anxiety: -1 vs -1 Hyperactivity: 0 vs -2 Social ability: 0 vs 0 Parent/teacher questionnaire: 0 vs -1 <u>Parent Questionnaire</u> Total score: -11 vs -8 Conduct Problem: -2 vs 0; p<0.05 Anxiety: -1 vs -2 Impulsive/Hyperactive: -2 vs 0 Learning problem: 0 vs 0 Psychosomatic: -1 vs 0 Perfectionism: 0 vs 0 Antisocial: 0 vs 0 Muscular tension: -1 vs 0 Parent/Teacher Questionnaire: -2 vs -1	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	NR	

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Wigal 2005 StART study US (Fair)	Male or female aged 6 to 12 years; diagnosis of DSM-IV-TR ADHD combined subtype or predominantly hyperactive/impulsive subtype; weight between 40 lb and 120 lb at enrollment; and capable of understanding and following classroom instruction and generally functioning academically at age-appropriate levels	Atomoxetine: wk1=0.5 mg/kg/d; wk2-3=1.2 mg/kg/d Mixed amphetamine salts (MAS) XR: wk1=10 mg; wk2=20 mg; wk3=30 mg (mean dosages NR) Duration=3 weeks (wk)	NR	Mean age=8.7 years 71.9% male 55.6% white 16.2% black 19.7% Hispanic 2.0% Asian or pacific islander 6.4% other	ADHD subtype Hyperactive/impulsive: 0.5% Combined: 99.5% CGI-S category: Borderline impairment: 2.5% Mildly impaired: 3.9% Moderately impaired: 60.1% Markedly impaired: 25.6% Severely impaired: 9.3%	215	25 (12.3%) withdrawn/lost to FU NR/203 (94.4%) (MAS XR n=102; atomoxetine n=101)

Evidence Table 1. Data abstraction of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wigal 2005 StART study US (Fair)	MAS XR vs atomoxetine SKAMP scale mean changes Deportment: -0.56 vs -0.13; p<0.0001 Attention: -0.49 vs -0.08; p<0.0001 SKAMP scale responders Deportment (≥ 25% improvement): 70% vs 38%; p≤0.0001 Attention (≥ 25% improvement): 68% vs 28%; p<0.0001 Math problems (mean number) Attempted: 62.6 vs 30.5; p<0.0001 Completed correctly: 61.6 vs 29.0; p<0.0001 CGIS-P mean decrease in unit points: -8.3 vs -6.63; p=NS CGI-I ratings of very much improved/much improved (% pts): 74.5% vs 35.6%; p<0.0001 PedsQL total score mean increase in unit points: +7.1 vs +7.9; p=NS PedsQL school functioning score increase in unit points (% increase): +34% vs +25%; p=0.0026 Parent-Rated Med-SS: MAS XR=atomoxetine (data NR)	MAS XR vs atomoxetine (p-values NR for all; those reported below reflect Oregon EPC calculations using StatsDirect) Overall AE incidence: 85% vs 73.1%; NS Upper abdominal pain: 18.7% vs 14.8% Vomiting: 4.7% vs 13%; p=0.035 Fatigue: 1.9% vs 7.4% Nausea: 6.5% vs 9.3% Weight decrease: 5.6% vs 3.7% Anorexia: 16.8% vs 9.3% Appetite decrease: 28% vs 17.6% Dizziness: 5.6% vs 1.9% Headache: 15% vs 10.2% Somnolence: 4.7% vs 18.5%; p=0.0015 Insomnia: 28% vs 7.4%; p<0.0001	Overall withdrawals: 13.1% vs 10.2%; NS AE withdrawals: 6.5% vs 3.7%; NS	In part by NIMH award MH02042 and a grant from Shire	

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Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Wolraich 2001 US (Fair)	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)	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	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	312	Withdrawn=206 (66%)/Lost to follow-up=1(0.3%)/Analyzed=277 (MPH n=94, MPH OROS n=94, Placebo n=89)

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Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wolraich 2001 US (Fair)	Mean change in IOWA Conners Scores (OROS MPH vs IR MPH) (p-values NR, but narrative states there are NS differences): <u>Teacher/Parent scores:</u> Inattention/Overactivity: -3.76/-4.79 vs -3.59/-3.73 Oppositional/Defiance: -1.6/-3.24 vs -1.3/-2.36 <u>Mean changes in secondary measures of efficacy (teacher ratings)</u> Peer Interaction: -0.33 vs -0.21 SNAP-IV Inattention: -0.69 vs -0.80 SNAP-IV Hyperactivity/Impulsivity: -0.64 vs -0.69 SNAP-IV Oppositional Defiant Disorder: -0.36 vs -0.32 Global Efficacy at end of study: 1.42 vs 1.43 <u>Mean change in secondary measures of efficacy (parent ratings)</u> SNAP-IV Inattention: -0.91 vs -0.77 SNAP-IV Hyperactive/Impulsive: -0.91 vs -0.74 SNAP-IV Oppositional Defiance Disorder: -0.65 vs -0.41 Global Efficacy at end of study: 1.47 vs 1.28 <u>Investigator ratings</u> Mean CGI at end of study: 4.24 vs 4.19 % of patients on CGI rated as "much" or "very much" improved: 46.7% vs 47.2% <u>Other</u> Global assessment of efficacy, % patients teachers/parents rated as "good or excellent": 42.9%/54.0% vs 46.9%/46.5% CGI, % patients rated as "very much improved or much improved": 46.7% vs 47.2% Parent Satisfaction Questionnaire (% pleased/very pleased/extremely pleased): 62.6% vs 64%	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%)	Alza	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 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Amiri 2008	Yes	Yes	Unclear (inadequate data presented)	Yes	Yes	Yes	Yes	Yes
Arnold 1978 Huestis 1975	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes
Barkley 2000	NR	NR	Crossover	Yes	Yes	Yes	Yes	No
Barrickman 1995	NR	NR	N/A - crossover	Yes	Yes	Yes	Yes	No; 3 (16.7%) excluded from analysis that were dropped due to failure to cooperate
Bergman 1991	Inadequate (counterbalanced order)	NR	N/A - crossover	No	Yes	Yes	Yes	Unclear
Biederman 2007	Randomization stated, but method NR	Unclear	Yes	Yes	Unclear; "double-blind" stated	Unclear; "double-blind" stated	Yes	Yes
Borcherding 1990	NR	NR	Crossover	Yes	Yes	Yes	Yes	No
Castellanos 1997	NR	NR	Crossover	Yes	Yes	Yes	Yes	No
Conners 1980	NR	NR	No	Yes	Yes	Yes	Yes	Unclear

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Amiri 2008	No	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Fair
Arnold 1978 Huestis 1975	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Barkley 2000	1 excluded due to low IQ	*Not rated*	NR	Reported that 20 - 31% completed each randomized order of drug administration	*Not rated*	*Not rated*	Poor
Barrickman 1995	No	*Not rated*	NR/NR	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Bergman 1991	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Biederman 2007	No	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Fair
Borcherding 1990	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Castellanos 1997	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Conners 1980	No	*Not rated*	Unclear	NR NR NR NR	*Not rated*	*Not rated*	Fair

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Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Connor 2000	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes
Connor 2000	Unclear; 3 subjects refused MPH alone and were "partially randomized" to other arms.	Unclear, no details	Unclear; The Total Teacher CBCL was 4.9 points different between monotherapy groups.	Yes	Yes for teachers and research assistants; probably not for parents due to EKGs only in clonidine groups	Probably not due to EKGs only in clonidine groups	Probably not due to EKGs only in clonidine groups	Unclear; 3/25 (12.5%) non-completers, but no details about how handled in analyses
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)	No
Efron 1997	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes
Efron 1998	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes
Elia 1990	NR	NR	Crossover	Yes	Yes	Yes	Yes	Unclear
Elia 1991	NR	NR	Crossover	Yes	Yes	Yes	Yes	Unclear
Elia 1993	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Connor 2000	No	*Not rated*	No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Connor 2000	*Not rated*	Unclear; 12.5% non-completers but no details about N analyzed	*Not rated*	*Not rated*	Unclear, "all subjects were acceptably compliant", unclear	Yes, No (MPH only=12.5%, clonidine only=25%)	Poor
Cox 2004	No	*Not rated*	No/No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Efron 1997	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Efron 1998	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Elia 1990	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Elia 1991	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Elia 1993	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Findling 2006	Unclear; randomized in a ratio of 3:3:1 (p 452)	NR	Yes, for treatment arms; O/D component of IOWA Conners' Scale lower (better) in placebo group compared to either treatment group	Yes	NR	Yes	Yes	Yes; stated in results, no data provided
Findling 2008	Yes	Unclear	Mostly, except for prior ADHD medication use, which was slightly higher in the MTS group	Yes	Yes	Yes	Yes	Not true ITT but small # not included. However, numbers in text and on figure disagree on how many not included.
Fitzpatrick 1992	Unclear. No use of "randomized" terminology; No description whatsoever of group assignment	NR	N/A - crossover	No	Yes	Yes	Yes	Unclear
Gau 2006	NR	NR	Yes	Yes	Partial; parent reporters knew which medication, teachers reporters did not	NR	No	Yes

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Findling 2006	Yes; 6 based on clinician's judgment (5 in placebo; 1 in MPH-IR)	*Not rated*	No/No; Placebo group had a high % of study withdrawal compared to the two treatment arms; withdrawal data on page 454.	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Findling 2008	Several patients withdrew after being randomized, but prior to having at least 1 primary efficacy assessment (planned for 1 week after dose optimization) = 3-4% of total. Not reported which groups these had been randomized to.	*Not rated*	Yes (62% of placebo group withdrew compared to 27.5% in both MTS group and MOS group) Yes (all groups >20% withdrew)	Yes/NR	*Not rated*	*Not rated*	Fair/Poor
Fitzpatrick 1992	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Gau 2006	No	*Not rated*	No/No	Yes Yes Yes No IR MPH group had less adherence than the OROS MPH group ($p < 0.0001$); report states this did not change the results	*Not rated*	*Not rated*	Fair

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Gross 1976	NR	NR	Crossover	Yes	Yes	Yes	Yes	No
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 for some efficacy measures; No for CPS and side effects
Kauffman 1981	NR	Yes	Crossover	Yes	Yes	Yes	Yes	Yes
Kemner 2005	NR	NR	No; OROS patients with greater severity of illness at baseline (ADHD-RS 39.9 vs 38.6; p=0.006); adjusted for this difference in the analysis	Yes	NR	No	No	NR
Kratochvil 2002	NR	NR	Yes	Yes	Yes	Yes	Yes	No; 10 (4.4%) excluded from analysis due to not having a post-baseline visit
Kuperman, 2001 U.S.	Method not reported	Method not reported	Yes	Yes	Yes but method not described	Not reported	Yes	No: 81.1%
Lopez 2003	NR	NR	N/A - crossover	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Gross 1976	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
James 2001	No	*Not rated*	NR/NR	Yes NR NR NR	*Not rated*	*Not rated*	Poor
Kauffman 1981	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Kemner 2005	NR	*Not rated*	NR	NR Yes NR NR	*Not rated*	*Not rated*	Poor
Kratochvil 2002	No	*Not rated*	No/No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Kuperman, 2001 U.S.	No	*Not rated*	No/No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Lopez 2003	No	*Not rated*	None	Yes NR NR NR	*Not rated*	*Not rated*	Fair

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
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	Yes
McCracken 2003	Unclear; Latin square design;	Yes; randomization schedules generated by the sponsor and distributed to the onsite pharmacist	N/A - crossover	Yes	Yes; states double blind but no details	Yes; states double blind but no details	Yes; states double blind but no details	Yes
Muniz 2008	Yes	Yes	NR (only means for whole group given, not separated by group to see how they compare)	Yes	Unclear - "double blind"	Yes	Yes	Yes
Newcorn 2008	Randomization stated, but method NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Palumbo 2008	Yes	Yes	Unclear; clonidine group had highest proportions of whites, family history of ADHD, and prior stimulant treatment	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Manos 1999	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
McCracken 2003	No	*Not rated*	No/No	Yes Yes Yes No	*Not rated*	*Not rated*	Fair
Muniz 2008	No	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Fair
Newcorn 2008	No	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Good/Fair
Palumbo 2008	*Not rated*	Yes	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Overall=No (36%) Between-groups=No (placebo=67%, MPH=38%, clonidine=16%, combination=25%)	Fair

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Pelham 2011	Unclear	Unclear	Unclear, no comparison based on order of randomization (crossover trial)	Yes	Unclear	Yes, double-dummy	Yes, double-dummy	No; exclusion of 1/10 (10%) of patients
Pelham 1987	NR	NR	N/A - crossover	Yes	Yes	Yes	Yes	Unclear
Pelham 1990	NR	NR	N/A - crossover	Yes	Yes	Yes	Yes	Unclear
Pelham 1999a	NR	NR	Crossover	Yes	Yes	Yes	Yes	Unclear
Pelham 1999b	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes
Pelham 2001	Yes	Yes for patients	N/A - crossover	Yes	Yes	Yes	Yes	No; 2 patients excluded (2.8%)
Pliszka 2000 Faraone 2001	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes
Prasad 2007	NR	NR	No, higher proportion with inattentive subtype in Atomoxetine group (11.5%) vs control (3.1%)	Yes	No	No	No	Unclear - modified ITT stated, appears only 75% of atomoxetine group included in analysis, while 94% of control group

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Pelham 2011	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Yes; Yes	Fair
Pelham 1987	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Pelham 1990	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Pelham 1999a	Unclear	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Pelham 1999b	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Pelham 2001	No	*Not rated*	NR/NR	Yes, NR, Yes (virtually 100%), NR	*Not rated*	*Not rated*	Fair
Pliszka 2000 Faraone 2001	No	*Not rated*	No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Prasad 2007	Yes; No	*Not rated*	Yes (discontinuation from trial 25% atomoxetine, 6% control No	Yes NR NR NR	*Not rated*	*Not rated*	Poor

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Sangal 2006	NR	NR	N/A - crossover; reported no differences at baseline	Yes	Yes; states double blind but no details	Yes; states double blind but no details	Yes; states double blind but no details	No
Schachar 2008	Yes	Yes	NR	Yes	Unclear - "double blind"	Unclear - "double blind"	Yes	Yes
Sharp 1999	NR	NR	Crossover	Yes	Yes	Yes	Yes	Yes
Silva 2005	Unclear; For counterbalancing, 10 crossover treatment sequences used; Williams design to control for effects of treatment order and relative position.	NR	NR; only data on entire study group	Yes	Yes	No; those dispensing medication not blinded	Yes; although states some might have known what they were taking	Unclear
Simpson 1980	NR	NR	N/A - crossover	Yes	Yes	Yes	Yes	Yes
Spencer 2011	Unclear	Yes, "…by the MGH Research Pharmacy"	Unclear; in OROS group, fewer were completely satisfied (33% vs 58%) and more had no adverse events (51% vs 33%)	Yes	Yes for efficacy, no for adverse events	Unclear, described as single-blind, but no information about capsule appearance and how concealed multiple daily dosage regimen from single daily dosage regimen	Same as care provider	Yes

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Sangal 2006	Yes; 35 due to low actigraphy scores or equipment malfunction	*Not rated*	No/No	Yes Yes Yes No	*Not rated*	*Not rated*	Poor
Schachar 2008	No	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Fair
Sharp 1999	No	*Not rated*	NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Silva 2005	No	*Not rated*	No/No	No No No No	*Not rated*	*Not rated*	Fair
Simpson 1980	No	*Not rated*	No	NR NR NR NR	*Not rated*	*Not rated*	Fair
Spencer 2011	*Not rated*	Unclear, reasons for noncompletion NR	*Not rated*	*Not rated*	Unclear, no for OROS-MPH group (complete compliance=46%), unclear	Yes, No (IR-MPH=8%, OROS-MPH=20%)	Fair

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Steele 2006	Yes; Site randomization lists	Yes	Yes	Yes	No	No	Yes	Yes
Stephens 1984	Not randomized; medication was prescribed by each child's physician (method NR)	N/A	N/A - crossover	No	Yes	Yes	Yes	Unclear
Swanson 2004	NR	NR	N/A - crossover	Yes	Yes	Yes	Yes	Yes
Taylor 2001	Unclear	Unclear	Unclear; no comparison of characteristics based on order of randomization to crossover design	Yes	Unclear; unmarked capsules used, but use of crossover design and once daily dosing of short-acting drugs may have increased risk of detecting drug assignment	Unclear; unmarked capsules used, but use of crossover design and once daily dosing of short-acting drugs may have increased risk of detecting drug assignment	Unclear; unmarked capsules used, but use of crossover design and once daily dosing of short-acting drugs may have increased risk of detecting drug assignment	Yes (df=16 for ANOVA in Table 1)
Taylor, 2000 U.S.	Method not reported	Method not reported	Not reported	Yes	Yes but method not described	Not reported	Yes	No: 95.4%

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Steele 2006	NR	*Not rated*	No/No	Yes/NR/Y/NR % of subjects who missed any dose during the trial was higher with IR-MPH (84%) than OROS-MPH (56%).	*Not rated*	*Not rated*	Poor
Stephens 1984	Unclear	*Not rated*	NR/NR	NR NR NR NR	*Not rated*	*Not rated*	Poor
Swanson 2004	No	*Not rated*	NR/NR	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Taylor 2001	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Unclear, Unclear	Fair
Taylor, 2000 U.S.	No	*Not rated*	No/ no	Yes NR NR NR	*Not rated*	*Not rated*	Fair

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Taylor, 2001 U.S.	Method not reported	Method not reported	Not reported	Yes	Yes but method not described	Not reported	Yes	Yes
Tourette's Syndrome Study Group 2002	Yes	Yes	No, MPH group had higher age (10.7 vs 9.7 yrs) and maturity (19% vs 9% pubescent), fewer children with inattentive subtype (65% vs 76%) and lower Conners ASQ-Teacher score (13.2 vs 16.4)	Yes	Yes double dummy assessors were parents and teachers	Yes, double-dummy	Yes, double-dummy	Yes, LOCF
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
van der Meere 1999	Unclear	Unclear	Unclear; fewer boys in placebo group (placebo=66%, MPH=94%, clonidine=100%); very few baseline characteristics reported (sex, age, IQ)	Yes	Yes, explicit statement	Yes, explicit statement	Yes, explicit statement	Yes

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Taylor, 2001 U.S.	No	*Not rated*	No/ no	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Tourette's Syndrome Study Group 2002	*Not rated*	Yes	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Yes (14%); Yes across treatment groups (range, 11% to 12%), but higher in placebo group (22%)	Fair
Tourette's Syndrome Study Group 2002	No	*Not rated*	No/No	Yes NR NR NR	*Not rated*	*Not rated*	Fair
van der Meere 1999	*Not rated*	Yes	*Not rated*	*Not rated*	Yes, Unclear, Unclear	No attrition	Fair

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
van der Meere 1999	NR	NR	Boys and girls were not equally distributed among the groups	No	Yes	Yes	Yes	Yes
Wang 2007	Randomization stated, but method NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Weiss 2007	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes
Whitehouse 1980	NR	NR	No, SR/IR on Overt signs of tension and IR>SR on tension/Anxiety	Yes	Yes	Yes	Yes	No, 4 (11.8%) excluded from analysis; not stated which groups these 4 were assigned to
Wigal 2005	NR	NR	Yes	Yes	Yes	Yes	Yes	No; 12 (5.6%) excluded from analysis; reasons for exclusion unclear
Wolraich 2001	Yes	Yes	Small differences (NS): proportions with comorbidities, prior MPH IR use, inattentive vs combined ADHD	Yes	Yes	Yes	Yes	Yes

Evidence Table 2. Quality assessment of head-to-head trials in children and adults with attention deficit hyperactivity disorder

Study	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
van der Meere 1999	No	*Not rated*	NR/NR	NR NR NR NR	*Not rated*	*Not rated*	Fair
Wang 2007	NR	*Not rated*	No/Yes MPH group had more complete than atomoxetine group (91.6% vs 84.1%; p=0.044)	Y/NR	*Not rated*	*Not rated*	Fair
Weiss 2007	NR	*Not rated*	No/No	Yes/NR	*Not rated*	*Not rated*	Fair
Whitehouse 1980	Yes, 4 excluded from analysis for: 2 dosage deviations, 1 viral illness, 1 "other reasons"	*Not rated*	None/None	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Wigal 2005	NR	*Not rated*	None	Yes NR NR NR	*Not rated*	*Not rated*	Fair
Wolraich 2001	No	*Not rated*	No/No	Yes NR NR NR	*Not rated*	*Not rated*	Fair

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Ahmann 2001 (Fair)	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; met the criteria of a Ritalin responder.	Adderall 0.3 mg/kg and 0.15 mg/kg doses, and placebo, 3 times per day, in 7 day cycles, in 2 weeks trials.	NR	n=79 ethnicity NR ages 10-15y 79.7% males	NR	NR	NR/NR/79
Allen 2005	Study subjects were children or adolescents at least 7 years of age but less than 17 years and 6 months and weighing between 20 and 80 kg at the time informed consent was obtained. All study subjects met DSM-IV criteria for ADHD and had concurrent Tourette syndrome or chronic motor tic disorder, as diagnosed by clinical interview and examination by the investigator and confirmed by the Schedule for Affective Disorders and Schizophrenia for School-age Children–Present and Lifetime Version16 (K-SADSPL).	Atomoxetine for up to 18 weeks: Mean Dose = 1.33 mg/kg/day (SD 0.22) Dose Range = 0.5 to 1.5 mg/kg/day (maximum total daily dose of 110 mg)	diphenhydramine allowed for insomnia	Mean age=11.2 yrs (SD 2.5 yrs), range 6.6 - 17.4 yrs 88.5% male 87.8% white	n(%), all NS ADHD subtype combined: 90(60.8), inattentive: 53 (35.8), hyperactive/impulsive: 5(3.4) Oppositional Defiance Disorder: 32(21.6) Major Depression: 1(0.7) Generalized anxiety disorder 5(3.4) Obsessive Compulsive Disorder 4 (2.7) previous exposure to stimulant therapy 101(68.2) Comorbidity: 100% ADHD and either chronic motor tic disorder, chronic vocal tic disorder or Tourette disorder (some patients list more than one diagnosis) Tourette disorder: 117 (79%) Chronic motor tic disorder: 44 (29.7%) Chronic vocal tic disorder: 26 (17.6%)	148	83/2/148

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
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 Nail biting: 26.7 vs 36.0, NS	"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.	Marshfield Clinic grants 0844-01-87 and 0844-01-90	the study includes the largest group of girls with ADHD reported in the literature (n=45)
Allen 2005	Tics efficacy, Atomoxetine vs. Placebo, change mean Yale Global Tic Severity Scale (YGTSS) total score: -5.5 vs. -3.0, p=0.063 YGTSS Motor: -3.1 vs. -1.7, p=0.119 YGTSS Phonic: -2.4 vs. -1.3, p=0.168 TSSR: -4.7 vs. -2.9, p=0.095 CGI-Tic/Neuro-S: -0.7 vs. -0.1, p=0.002 ADHD/Behavior Efficacy, change mean ADHD-RS Total: -10.9 vs. -4.9, p=0.002 ADHD-RS Inattentive: -5.7 vs. -2.7, p=0.019 ADHD-RS hyperactive/impulsive: -5.2 vs. 2.1, p=0.002 CGI-ADHD/Psych-S, -0.8 vs. -0.3, p=0.015 CGI-Overall-S, -0.6 vs. -0.2, p=0.014	No serious AE Atomoxetine vs. Placebo, N (%) Headache, 16 vs. 14, p=0.840 Vomiting, 12 vs. 6, p=0.211 Upper abdominal pain 7 vs. 9, p=0.601 decreased appetite 12 vs. 2, p=0.01 Cough 4 vs. 9, p=0.151 Nausea 12 vs.1, p=0.002 Fatigue 9 vs.3, p=0.131 Pharyngitis 3 vs. 9, p=0.073 Diarrhea 3 vs. 8, p=0.123	Atomoxetine vs. Placebo 50 vs. 53; 2 vs. 1 withdrawals due to AE	Eli Lilly	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Arnold 2004 (Poor)	Children and adolescents with ADHD based on DSM-III-R	Dexmethylphenidate 5-20mg/day Duration: 6 weeks	NR	MPH group: n=35 Mean age=10.1 years Gender: 85.7% male Ethnicity: 80% Caucasian, 14.3% African-American, 5.7% Hispanic Placebo group: n=40 Mean age=9.9 years Gender: 77.5% male Ethnicity: 75% Caucasian, 12.5% African-American, 12.5% Hispanic	d-MPH: placebo Teacher SNAP-ADHD- 0.7: 0.7 Parent SNAP-ADHD- 0.65: 0.55 ADHD type Inattentive- 7(20%): 8(20%) combined- 28(80%): 32(80%) Stimulant naïve- 29(82.9%): 25(62.5%)	89	5/3/75 6 with other reasons
Bangs 2007	Adolescents aged 12-18 years who met the criteria for both ADHD and MDD per the DSM-IV as confirmed by the K-SADS-PL; score of at least 1.5 SD's above age and sex norms on ADHD-RS-IV; Children's Depression Rating Scale-Revised (CDRS-R) total score of at least 40 at every visit prior to randomization	Study period I: screening/baseline assessment Study period II: 1-week placebo lead-in (blinding unclear) Study period III: Atomoxetine 1.51 mg/kg QD (mean final dose) vs placebo x 9 weeks	No other psychotropics allowed	Mean age=14 73% male 82% white	ADHD Subtype Combined: 43% Inattentive: 57% Prior stimulant exposure: 81% Height (cm): 163.7 Weight (kg): 61	141	22 (15%) withdrawn/4 (2.8%) lost to FU/140 analyzed

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
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).	46% of d-MPH patients and 38% of placebo patients experienced at least one AE, which is generally mild.	NR	Celgene	
Bangs 2007	Atomoxetine vs placebo ADHD-RS-IV-Parent: Inv Mean Change: -13.3 vs -5.1; p<0.001 CDRS-R mean change: 53.4 vs 52; NS CGI-I score of 1 or 2 (% pts): 33 (48%) vs 12 (18%); p<0.001 CGI-S score of 1 or 2 (% pts): 13 (19%) vs 7 (10%), NS	Atomoxetine vs placebo (% pts) Headache: 12 (17%) vs 7 (10%), NS Nausea: 16 (22%) vs 4%), p=0.002 Vomiting: 9 (12%) vs 6 (9%), NS Fatigue: 9 (12%) vs 3 (4%), NS Upper abdominal pain: 6 (8%) vs 5 (7%), NS Dizziness: 9 (12%) vs 2 (3%), NS Decreased appetite: 9 (12%) vs 0; p=0.003 Diarrhea: 1 (1%) vs 6 (9%), NS Influenza: 3 (4%) 4 (6%), NS Pyrexia: 2 (3%) vs 5 (7%), NS Weight decreased: 6 (8%) vs 1 (1%), NS Irritability: 4 (6%) vs 1 (1%), NS Weight increased: 1 (1%) vs 4 (7%), NS	Overall withdrawals: 13 (18%) vs 9 (13%), NS Withdrawals due to AE: 1 (1%) vs 1 (1%), NS	Eli Lilly & Company	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Bangs 2008 Europe & Australia	Patients were 6-12 years and met DSM-IV criteria for ADHD (any subtype) and comorbid ODD. If other comorbid conditions were present, either ADHD or ODD was the primary diagnosis.	Atomoxetine 1.2mg/kg; once daily Placebo 8 weeks	NR	Atomoxetine vs Placebo Mean age (years): 9.5 vs 9.7 91.7% vs 97.1% males Ethnicity: NR	Atomoxetine: n=156 Previous stimulant exposure: 66.7% Mean height: 136.6cm Mean weight: 33.2kg Placebo: n=70 Previous stimulant exposure: 74.3% Mean height: 139.3cm Mean weight: 36.3kg <u>Atomoxetine vs Placebo</u> ADHD combined type: 84.6% vs 84.3% ADHD inattentive type: 9.0% vs 11.4% ADHD hyperactive/impulsive type: 6.4% vs 4.3%	257/226/226	29 total (24, 15% from atomoxetine group and 5, 7% from placebo group) 1 lost to follow-up from placebo group 257 analyzed

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Bangs 2008 Europe & Australia	**Atomoxetine vs Placebo (mean change)** <u>SNAP-IV</u> ODD: -3.7 vs -2.9 Combined: -9.6 vs -4.4 (p<0.001) Inattentive: -5.0 vs -2.2 (p<0.001) Hyperactivity/impulsivity: -4.6 vs -2.2 (p=0.003) CGI-I: 3.5 vs 3.9 (p=0.037) CGI-S: -0.7 vs -0.3 (p=.013) <u>ADHD impact module</u> Child: 10.2 vs 2.5 (p=.002) Child self-control: 0.13 vs 0.17 (NS) Family: 9.4 vs 3.5 (p=0.018) <u>CGI-P</u> Total: -4.7 vs -1.6 (p=0.002) Restless/impulsive: -3.7 vs -1.2 (p<0.001) Emotional lability: -1.0 vs -0.4 (NS)	NR	29 withdrawals 6 (3.8%) for AEs in Atomoxetine group 0 for AEs in placebo group	Many authors receive funding from Eli Lilly	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Barkley 1988 (Fair)	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 established through developmental/medical histories and observation of the children	methylphenidate 0.15mg/kg bid or 0.5mg/kg bid or placebo Duration: 7-10 days for each condition (baseline, placebo, low dose, high dose) Timing: NR	NR	Mean age=3.9 years Gender: 70.3% male Ethnicity: NR	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)	27	0/0/27

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
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	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	NIMH Grant # MH 32334; Department of Neurology, Medical College of Wisconsin	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Biederman 2002/Subgroup Analysis of Girls from Michelson 2001	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.	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)	No	Mean age in years: 9.66 Males = 0% Ethnicity = NR	Diagnostic subtypes: -Inattentive = 21.2% -hyperactive /impulsive =0% -Combined = 78.8% Mean Scores: WISC Full Scale IQ = 105.2 ADHD RS Total T-Score = 88.9 ADHD RS (Total) = 38.2 ADHD RS Inattentive subscale = 21.4 ADHD RS Hyperactive/Impulsive subscale = 16.7 CPRS-R ADHD index = 26.9 CGI-ADHD-S = 4.8 Oppositional/defiant disorder: 38.5% Phobias: 13.5%	291	1/NR/51

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms			Total withdrawals; withdrawals due to adverse events	Funding	Comments
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 significant 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		Atom.(n=31)*	Placebo(n=21)*	3 withdrawals/ 2 due to AE's	Lilly	
		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) 1 patient withdrew from each group due to AE's - one had chest pain, the other had somnolence					

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Biederman 2005	Patients were 6 to 17 years of age and had a diagnosis of ADHD on the basis of criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) for ADHD at screening, as manifested by a psychiatric/clinical evaluation and the Diagnostic Interview Schedule for Children, Fourth Edition, with a Clinical Global Impression Severity of Illness (CGI-S) rating of 4 or higher ("moderately ill" or worse). In addition, patients were attending full-time school (i.e., they were not being homeschooled); had a teacher-/investigator-rated Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version total and/or subscale score at least 1.5 SDs above normal values for age and gender, were between the 5th and 95th percentile for weight and height on the basis of National Center for Health Statistics guidelines, had an IQ of at least 80 as estimated by the Wechsler Intelligence Scale for Children–Third Edition, and had a score of at least 80 on the Wechsler Individual Achievement Test–Second Edition–Abbreviated.	Modafinil Mean Dose: 368.5 mg Dose Range: 170–425 mg once daily	none/NR	Mean age=10.3 years 71% male Ethnicity NR	No Statistically significant between-group differences were observed for any characteristic at baseline. **CGI-S Score, N (%)** Moderately ill: 115 (47) Markedly ill: 93 (38) Severely ill: 37 (15) Among the most extremely ill: 1 (0.4) **Current ADHD subtype, N (%)** Inattentive: 94 (38) Hyperactive-Impulsive: 7 (3) Combined: 145 (59) **Previous ADHD treatment, N (%)** MPH-MPH HCL: 83 (34) Dexamphetamine Sulfate: 64 (26) Atomoxetine HCL: 35 (14) Other: 12 (5) **No previous ADHD treatment:** 133 (54) **Most frequently co-administered agents in >10% of patients N (%)** Non-opioid analgesics/Anti-inflammatories: 76 (31) Respiratory Agents: 49 (20) Anesthetics: 41 (20) Antihistamines: 34 (14) Other: 95 (39) **ADHD-RS-IV Total score Mean** School Version: 35.7 Home Version: 37.43	248	118/7/244

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Biederman 2005	Modafinil vs. Placebo, change (p value) **CGI-S Score, N (%)** Moderately ill: 115 (47) Markedly ill: 93 (38) Severely ill: 37 (15) Among the most extremely ill: (0.4) **Current ADHD subtype, N (%)** Inattentive: 94 (38) Hyperactive-Impulsive: 7 (3) Combined: 145 (59) **Previous ADHD treatment, N (%)** Methylphenidate-Methylphenidate Hydrochloride: 83 (34) Dexamphetamine Sulfate: 64 (26) Atomoxetine Hydrochloride: 35 (14) Other: 12 (5) **No previous ADHD treatment:** 133 (54) **Most frequently co-administered agents in >10% of patients N (%)** Non-opioid analgesics/Anti-inflammatories: 76 (31) Respiratory Agents: 49 (20) Anesthetics: 41 (17) Antihistamines: 34 (14) Other: 95 (39) **ADHD-RS-IV Total score Mean** School Version: 35.7 Home Version: 37.43 **Modafinil vs. Placebo, change (p value)** **ADHD-RS-IV School Version** Total Score: -15 vs. 7.3(<.0001) Inattention: -8.8 vs. -5.0(<.0001) Hyperactivity-impulsivity: -6.3 vs. -2.3(<.0001) **ADHD-RS-IV Home Version** Total Score: -14.3 vs. -7.0(<.0001) Inattention: -7.9 vs. 3.8(<.0001) Hyperactivity-impulsivity: -6.4 vs. -3.3(.001)	Modafinil vs. Placebo N(%) Insomnia: 48(29) vs. 3(4), P<0.05 Headache: 32(20) vs. 12(15), NS Decreased Appetite: 26(16) vs. 3(4), P<0.05 Infection: 19(12) vs. 12(15), NS Rhinitis: 16(10) vs. 9(11), NS Pharyngitis: 14(9) vs. 5(6), NS Cough Increased: 13(8) vs. 7(9), NS Abdominal Pain: 12(7) vs. 9(11), NS Rash: 10(6) vs. 2(4), NS Vomiting: 10(6) vs. 7(9), NS Accidental Injury: 8(5) vs. 5(6), NS Nervousness: 7(4) vs. 5(6), NS Fever: 8(5) vs. 2(2), NS Pain: 8(5) vs. 1(1), NS Asthenia: 6(4) vs. 4(5), NS Somnolence: 4(2) vs. 4(5), NS	118/8	Cephalon Inc	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Biederman 2006	Children aged 6 to 13 years whose height and weight corresponded to greater than the fifth percentile in standardized growth charts and who were attending full-day kindergarten, elementary school, or middle school were eligible. Participants met complete criteria of the DSM-IV for ADHD (combined type, predominantly inattentive type, or predominantly hyperactive-impulsive type) at screening, as determined by a psychiatric/clinical evaluation and confirmed by the Diagnostic Interview Schedule for Children, Fourth Edition. At screening, an intelligence quotient (IQ) of at least 80, as estimated on the Wechsler Intelligence Scale for Children, Third Edition, and a score of 80 or higher on the screener version (for learning disabilities) of the Wechsler Individual Achievement Test were used to rule out low IQ or learning disabilities as contributing causes of symptoms and were required for inclusion.	Modafinil: Dose Range: Divided doses of 300/0 (300mg/day total), 200/100 (300mg/day total), 100/200 (300mg/day total), 200/200 (400mg/day total), or placebo	None/NR	Mean age=9.2 yrs (Range: 6 to 14 yrs) 75% male 81.4% Caucasian	**NS for all characteristics** **Current ADHD subtype N(%)** Combined: 190 (77) Inattentive: 51 (21) Hyperactive-impulsive: 5 (2) **CGI-S N(%)** Moderately ill: 107 (43) Markedly ill: 118 (48) Severely ill: 21 (8) Among the Most Extremely ill: 2 (0.8) **ADHD—RS-IV Mean, Score** **School Version** Total: 25.6 Inattention: 14.6 Hyperactivity-impulsivity: 11.4 **Home Version** Total: 36.1 Inattention: 19.8 Hyperactivity-impulsivity: 16.2 **CADS-P, Mean, Score** (t score) Total: 74.6 ADHD Index: 73.1 Inattentive: 72.1 Hyperactive-Impulsive: 73.8	248	22/4/196

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Biederman 2006	**RESULTS ESTIMATED FROM GRAPHIC** Mean (SEM) Changes From Baseline to the Final Visit on ADHD Rating Scales for the 300-mg Modafinil dosing groups. (MG) 300/0 vs. 200/100 vs. 100/200 vs. Placebo (p value) **ADHD-RS-IV, School Version** Total: -8.7(≤.01)/-7.9(<.05)/-5.3(NS)/-2.1(NS) Inattention: -4.8(≤.01)/-4(NS)/-2.7(NS)/-.5(NS) Hyperactivity-impulsivity: -4(<.05)/-3.9(<.05)/-2.7(NS)/-1.2(NS) **ADHD-RS-IV, Home Version** Total: -11.4(≤.001)/-8.1(NS)/-8(NS)/-3.8(NS) Inattention: -6(≤.01)/-4.1(NS)/-4.3(NS)/2(NS) Hyperactivity-impulsivity: -6.7(≤.001)/-4(<.05)/-3.8(NS)/-1.8(NS) **CADS-P** ADHD Index: -7.9(<.05)/-4.3(NS)/-7(NS)/4(NS) Total: -7.1(≤.01)/-6.2(NS)/-7.9(≤.01)/-2(NS) Inattentive: -7(<.05)/-4.8(NS)/-6.4(<.05)/-2.9(NS) Hyperactive-impulsive: -6.4(<.05)/-7(<.05)/-7(≤.01)/-1.6(NS) **Mean (SEM) Changes From Baseline to the Final Visit on ADHD Rating Scales for the 400-mg Modafinil dosing group. (Mg) 200/200 vs. Placebo (P Value)** **ADHD-RS-IV, School Version** Total: -5.4(NS) vs. -2.3(NS) Inattention: -3(NS) vs. -0.3(NS) Hyperactivity-impulsivity: -2.3(NS) vs. -2.1(NS) **ADHD-RS-IV, Home Version** Total: -10.2(.01) vs. -3.8(NS) Inattention: -5.4(.01) vs. -1.8(NS) Hyperactivity-impulsivity: -5(<.05) vs. -2(NS) **CADS-P** ADHD Index: -8.1(NS) vs. -4.1(NS) Total: -8.2(<.05) vs. -2.3(NS) Inattentive: -6.8(NS) vs. -2.9(NS) Hyperactive-impulsive: -8.8(<.05) vs. -2(NS)	**(MG) 200/200 vs. 200/100 vs. 100/200 vs. 300/0 vs. Placebo** Headache: 7(14)/6(12)/6(13)/7(14)/11(22) Insomnia: 5(10)/7(14)[p<.05]/6(13)/5(10)/1(2) Infection: 3(6)/1(2)/3(6)4(8)/6(12) Pain (Abdominal): 3(6)/5(10)/6(13)/4(8)/4(8) Cough: 2(4)/2(4)/3(6)/6(12)/2(4) Rhinitis: 2(4)/0(0)/5(10)/2(4)/2(4) Decreased Appetite: 1(2)/4(8)/3(6)/6(12)/1(2) Fever: 0(0)/5(10)/5(10)/2(4)/2(4)	22/9	Cephalon Inc	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Biederman 2007	Male and female children aged 6 to 12 years who met DSM-IV criteria for ADHD and ADHD-RS-IV score >= 28	LDX 30, 50, or 70 mg with forced-dose titration, or placebo 1 week screening 1 week wash out and 4 weeks treatment 30 mg for 4 weeks, 50 mg (30 mg/d for week 1, with forced-dose escalation to 50 mg/d for weeks 2-4), or 70 mg (30 mg/d for week 1, with forced-dose escalation to 50 mg/d for week 2 and 70 mg/d for weeks 3 and 4), or placebo all 4 weeks	None	Mean age: 9 yrs. 69% male 53% white	LDX 30 mg vs LDX 50 mg vs LDX 70 mg vs Placebo Combined n(%): 67 (94.4) vs 71 (95.9) vs 71 (97.3) vs 69 (95.8) Hyperactive n(%): 4 (5.6) vs 3 (4.1) vs 2 (2.7) vs 3 (4.2) Mean age of ADHD onset, yrs (SD): 6.9(2.2) vs 7 (2.3) vs 2 (2.2) vs 7.6 (2.2) Prior treatment, n (%) Amphetamine: 7 (9.9) vs 7 (9.5) vs 2 (2.7) vs 6 (8.3) MPH: 14 (19.7) vs 13 (17.6) vs 8 (11) vs 12 (16.7) Stimulant: 3(4.2) vs 3(4.1) vs 5 (6.8) vs 2 (2.8) Atomoxetine: 2 (2.8) vs 0 vs 2 (2.7) vs 1 (1.4) Stimulant/atomoxetine: 1 (1.4) vs 2 (2.7) vs 3 (4.1) vs 4 (5.6) Other: 2 (2.8) vs 1 (1.4) vs 2 (2.7) vs 1 (1.4) None (past 12 mo.): 42 (59.2) vs 48 (64.9) vs 51 (69.9) vs 46 (63.9)	290	60 withdrawals/ 11 / 285 analyzed

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Biederman 2007	At 4 weeks of treatment ADHD-RS-IV total score) was significantly greater with each of the 3 LDX doses compared with placebo (P < 0.001, d[= 3256, F = 35.16) (Data in graphs) Effect sizes based on the ADHD-RS-IV were LDX30 1.21, LDX50 1.34, and LDX70 1.60 (by the corresponding between-group differences and the model-based SD of 12.84). CPRS-R scores were significantly better in active groups than Placebo throughout study (P< 0.01, Data=NR) CGI-I ratings were either "very much improved" or "much improved" in _>70% of patients in the active-treatment groups, compared with 18% of patients receiving placebo. (Data= NR)	Treatment Emergent AEs (%) Any Events **LDX30 71.8 LDX50 67.6 LDX70 83.6** Placebo 47.2 Decreased appetite **LDX30 36.6 LDX50 31.1 LDX70 49.3** Placebo 4.2 Insomnia LDX30 15.5 LDX50 16.2 LDX70 24.7 Placebo 2.8 Irritability **LDX30 11.3 LDX50 8.1 LDX70 9.6** Placebo 0 Dizziness **LDX30 7.0** LDX50 5.4 LDX70 2.7 Placebo 0 Vomiting LDX30 7.0 LDX50 5.4 **LDX70 13.7** Placebo 4.2 Weight loss LDX30 5.6 LDX50 2.7 **LDX70 19.2** Placebo 1.4 Dry mouth LDX30 2.8 LDX50 2.7 **LDX70 8.2** Placebo 0 **P=< 0.05 compared to placebo**	LDX30 15 LDX50 14 LDX70 13 Placebo 18; LDX30 4 LDX50 4 LDX70 10 Placebo 1		

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Biederman 2007	Children and adolescents, aged 6–16, who met the criteria for ADHD in the DSM-IV, as confirmed by clinical assessment and structured interview. Subjects were required to have a symptom severity score that was at least 1.0 (study LYAW) or 1.5 (studies LYAT and LYBG) standard deviations above age and sex norms on the ADHD-RS-IV parent version: investigator-administered and -scored scale (ADHD-RS-IV-Parent:Inv) for either the total score or the inattention or hyperactivity/impulsivity subscale scores, corresponding to the combined, primarily inattentive, and primarily hyperactive/impulsive subtypes of ADHD, respectively. Subjects were assessed for lifetime psychiatric disorders, including ODD, by clinical history and structured interview, using the K-SADS-PL. Subjects with learning disabilities were not excluded. However, subjects were required to be of normal intelligence (IQ ≥80), as assessed by either the full Wechsler Intelligence Scale for Children, third edition (WISC-III), or the four specified subtests of the WISC-III (block design, picture arrangement, similarities, and vocabulary).	Once-daily atomoxetine (up to 1.8 mg/kg/day) or placebo Mean Dose: NR In two of the three studies, subjects assigned to atomoxetine received 0.8 mg/kg/day in the morning for 3 days, after which the dose was increased to 1.2 mg/kg/day. In the other study, subjects assigned to atomoxetine received 0.5 mg/kg/day for 3 days, followed by 0.75 mg/kg/day for the remainder of the first week; then, the dose was increased to 1.0 mg/kg/day. After 3–4 weeks, subjects with significant residual symptoms [defined by a clinical global impressions of severity (CGI-S) score of 3 or greater] and for whom there was no safety or tolerability contraindication could have their dose increased to 1.5–1.8 mg/kg/day.	NR	Mean age: 9.9 yrs 73.4% male Ethnicity: NR	ODD-comorbid vs non-comorbid, n(%) Conduct disorder: 13/151 (8.6) vs 0 (0), p = <.001 General anxiety disorder: 4/150 (2.7) vs 3/353 (0.9), p = 0.205 Major depressive disorder: 4/151 (2.7) vs 7/352 (2), p = 0.741 ODD-Comorbid vs non-comorbid, n (%): Hyperactive/impulsive: 1 (0.6) vs 8 (2.3) Inattentive: 22 (13.9) vs 141 (39.8) Combined: 135 (85.4) vs 205 (57.9)	512	NR/NR/512

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Biederman 2007	Youth with ODD exhibited greater ADHD severity than non-comorbid youth according to ADHD-RS-IV-Parent: Inv total scores (ODD-comorbid: 5.2+0.8 vs non-comorbid: 38.3+9.5) ADHD with ODD vs ADHD without ODD CGI-ADHD-S: 5.2+0.8 vs 4.7+0.7, p = 0.001 CPRS-R:S: 12.2+4.1 vs 7.4+4.5, p<0.001 CHQ Psychosocial summary scores: 27.9+10.2 vs 34.4+10.1, p<0.001	NR	NR	New River Pharmaceuticals and Shire	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Biederman 2008 SPD5O3 Study Group U.S. and U.K.	Patients aged 6-17, DSM-IV criteria for primary diagnosis of ADHD combined sub-type, predominantly inattentive subtype or predominantly hyperactive-impulsive subtype	A. Guanfacine ER 2mg B. Guanfacine ER 3mg C. Guanfacine ER 4mg D. Placebo for 16 weeks	NR	Age: 10.5 (6.0 to 17.0) % male: 74.5% White: 70.1% Black: 13.3% Hispanic: 9.9% Asian or Pacific Islander: 0.6% Native American: 0.3% Other: 5.8%	ADHD subtype: Inattentive: 26.1% Hyperactive-impulsive: 2.0% Combined: 71.9% Time since ADHD diagnosis, mean (range): 2.61 (0.0 to 13.0)	345	130/12/unclear

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Biederman 2008 SPD5O3 Study Group U.S. and U.K.	Mean reduction in ADHD-RS-IV score at endpoint across all Guanfacine ER groups vs placebo -16.7 vs -8.9, p<0.0001 Mean (95% CI) change from baseline(placebo adjusted) in ADHD-RS-IV total scores in guanfacine 2vs 3vs 4 mg : -7.70(-12.25 to -3.15), p=0.0002 vs -7.95(-12.50 to -3.40), p=0.0001 vs -10.39 (95% CI -14.97 to -5.82), p<0.0001 Mean change from baseline in hyperactivity/impulsivity score in placebo vs guanfacine 2mg vs 3 mg vs 4mg: -4.06 vs -6.94 vs -7.09 vs -9.46 LS mean change from baseline -3.51 vs -7.33 vs -7.32 vs -9.31 Placebo adjusted LS mean (95% CI) in 2mg, 3mg and 4mg groups: -3.82 (-6.05 to =1.59), p=0.0002 vs -3.81(-6.03 to -1.58), p=0.0002 vs -5.80 (-8.03 to -3.56), p<0.0001 Proportion of patients with CGI improvement at endpoint in placebo vs guanfacine 2, 3 and 4mg groups: 25.64% vs 55.95% vs 50.00% vs 55.56%, p(vs placebo)=0.01 for all guanfacine groups vs placebo at endpoint (p-values interpreted from graph). Mean change from baseline in combined subtype in placebo vs guanfacine 2mg, 3mg and 4mg: -8.45 vs -17.57 vs -15.38 vs -21.41 LS Mean (95%CI) change from baseline (placebo adjusted) in guanfacine 2mg, 3mg, 4 mg groups: -9.06 (-14.78 to -3.34), p=0.0007 vs -8.43 (-13.75 to -3.12), p=0.0007 vs -12.55 (18.10 to -7.00), p<0.0001 Mean change from baseline in inattentive subtype in placebo vs guanfacine 2mg, 3mg and 4mg: -10.44 vs -11.64 vs -17.59 and -13.30 LS Mean (95% CI) change from baseline (placebo adjusted) in guanfacine 2, 3 and 4mg groups: -3.95 (-6.54 to -1.36), p=0.0011 vs -4.19 (-6.78 to -1.60), p=0.0006, -4.52 (-7.13 to -1.90), p=0.0002	Placebo vs Guanfacine 2mg vs 3mg vs 4mg % patients with TEAE: 55 (64.0%) vs 67 (77%) vs 76 (88.4%) vs 75(87.2%) Upper abdominal pain: 5 (5.8) vs 9 (10.3%) vs 14 (16.3%) vs 14 (16.3%) Dry mouth: 1 (1.2%) vs 2 (2.3%) vs 8 (9.3%) vs 5 (5.8%) Nausea: 2 (2.3%) vs 6 (6.9%) vs 5 (5.8%) vs 5 (5.8%) Fatigue: 3 (3.5%) vs 16 (18.4%) vs 18 (20.9%) vs 13 (15.1%) Lethargy: 3 (3.5%) vs 5 (5.7%) vs 7 *8.1%) vs 8 (9.3%) Pyrexia: 3 (3.5%) vs 2 (2.3%) vs 0 (0%) vs 6 (7.0%)	Placebo vs Guanfacine ER 2mg vs 3mg vs 4mg Total withdrawals: 33/86 (38.4%) vs 29/87 (33.3%) vs 31/86 (36%) vs 37/86 (43%) Withdrawals due to AE: 1/33(3%) vs 9/29 (31%) vs 13/31 (42%) vs 20/47 (54.1%)	Shire Development Inc	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Brams 2008 U.S.	Males and females aged 6-12 years, who met the DSM-IV criteria for ADHD of any type, subjects must have been stabilized on a total daily dose or the nearest equivalent dose of methylphenidate 40-60mg or dexmethylphenidate 20-30mg for ≥2 weeks prior to screening.	Dexmethylphenidate ER 20mg/day Placebo	NR	Mean age: 9.5 years 61.6% male 48.8% Caucasian 24.4% Black 2.3% Oriental 23.3% Hispanic 1.2% other	Mean height: 137.8cm Mean weight: 37.0kg Duration of ADHD symptoms: 4.7 years ADHD combined type: 87.2% ADHD inattentive type: 2.8% ADHD hyperactive-impulsive type: 0%	92/86/86	NR
Brown 1988 (Fair)	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	methylphenidate 0.15mg/kg, 0.3mg/kg or 0.5mg/kg, bid or placebo (crossover) (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	NR	Mean age=13.5 year Gender: 100% male Ethnicity: black	WISC-R IQ=92.91(5.28) Parent rating on Conners factorial rating scale(total)=0.91(0.33) Teacher ratings abbreviated Conners hyperactivity Index=2.12(0.36)	11	0/0/11

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Brams 2008 U.S.	**Dexmethylphenidate ER vs Placebo** Mean change in SKAMP-Combined score 0.5 hours post dose: -0.969 vs 3.336 (p<0.001) Mean change in SKAMP-Combined score 1, 2, 4, 6, and 8 hours post dose was greater in dexmethylphenidate ER vs placebo (p<0.001 for all time points) Mean change in SKAMP-Attention and SKAMP-Deportment scores 0.5, 1, 2, 4, 6, and 8 hours post dose was greater in dexmethylphenidate ER vs placebo (p=0.012 and p=0.003 for 0.5 hours post dose for SKAMP-Attention and SKAMP-Deportment scores, respectively and p<0.001 for all other time points) Dexmethylphenidate ER was significantly more effective than placebo at all time points for both Math Test-Correct (p=0.001 at 0.5 hours post dose and p<0.001 at all other time points) and Math Test-Attempted (p=0.003 at 0.5 hours post dose and p<0.001 at all other time points)	Total: 17.4% while taking dexmethylphenidate ER and 22.1% while taking placebo Common AEs (dexmethylphenidate ER vs Placebo): abdominal pain: (upper) 3.5% vs 4.7% headache: 3.5% vs 2.3% increased appetite: 0% vs 3.5% gastroenteritis (viral): 0% vs 2.3%	NR	Novartis Pharmaceuticals Corporation	
Brown 1988 (Fair)	*28 out of 36 (75%) dependent measures resulted in significant main effects for drug condition Pairwise 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	number of side effect: only a significant difference was found in the comparison of 0.15mg/kg and 0.50mg/kg	0	NR	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Buitelaar 2007	Patients aged 6 to 15 years who met DSM-IV criteria for ADHD, as assessed by clinical history and confirmed by a structured interview (Schedule for Affective Disorders and Schizophrenia for School-aged Children-Present and Lifetime Version [K-SADS-PL]), and whose symptom severity was at least 1.5 standard deviations above US age and sex norms on the ADHD Rating Scale IV (ADHD RS) were eligible to participate. Patients with bipolar disorder or psychotic illness were excluded, as were patients with unstable medical illness or conditions requiring ongoing administration of a psychoactive medication (other than atomoxetine). Comorbid psychiatric disorders were assessed clinically and by the K-SADS-PL. All subjects had a medical evaluation including physical examination, routine chemistries, liver function tests, complete blood count, urinalysis, and electrocardiogram (ECG).	Atomoxetine vs. placebo 6 months	None	Mean age=10.8 yrs Gender: 90% male Ethnicity: NR	Population characteristics at 2nd randomization ADHD RS Total (mean): 40.8 ADHD RS Total T-score (mean): 80 ADHD-RS Inattention score (mean):21.5 ADHD-RS Hyperactivity/Impulsivity score (mean): 19.4 CTRS-RS ADHD Index: 23.7 CPRS-RS ADHD Index: 28.4 CDRS total score: 26.5 MASC Anxiety Disorder Index: 10.9 CHQ Psychological Summary score: 30.5	163	41/ NR/ 161

Evidence Table 3. Data abstraction of placebo-controlled trials in children

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Buitelaar 2007	Change from baseline active vs placebo ADHD-RS 1.7 vs. 7.8 (P < 0.001) Rates of relapse 2.5% vs. 12.2% (P = NR) RR for relapse during placebo treatment 5.6 (95% CI 1.2, 25.6)	NR	Total 27%; atomoxetine 17.7%;placebo 33.3% Due to AEs NR	Eli Lilly and Co.	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Chacko 2005 U.S.	5-6 year olds who met DSM-IV ADHD criteria and who were enrolled in the STP conducted at the Western Psychiatric Institute and Clinic or the University at Buffalo, SUNY.	Methylphenidate 0.3 mg/kd and 0.6 mg/kg (given bid) Placebo Medication given at 7:45 am and 11:45 am Monday-Thursday 6-week study Each treatment occurred 1-2 times/week, with the order randomized on a daily basis.	Medications: NR; in addition to medication, the children also had behavioral treatment in the STP.	Mean age: 6.13 years 89% male 86% white	Full scale IQ (SD): 102 (15.50) Parent-rated vs teacher-rated abbreviated Conners: 19.5 vs 18.8 IOWA Conners Rating (SD) Inattention/overactivity: 10.9 (3.9) Oppositional/defiant: 7.0 (4.5) 50% met DSM-III-R or DSM-IV criteria for ODD 27.8% met DSM-III-R or DSM-IV criteria for conduct disorder (CD)	NR / NR/ 36	0 / 0 / 36

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Chacko 2005 U.S.	Dose effects were significant for 2 of the 4 point system measures: % following activity rules, p<0.001 Non-compliance, p<0.001 Dose effect was significant for 1 of the 3 classroom measures: % following activity rules, p<0.05 For the point system, these measures were statistically significant for both doses vs. placebo (p<0.05) % following activity rules, non compliance, conduct problems, and negative verbalizations For the classroom measures, % following classroom rules and seatwork completed were statistically significant for both doses vs. placebo (p<0.05) but % seatwork correct was not significantly different for either dose vs placebo.	The only common side effect was appetite loss at lunch, with counselors reporting it for 2 in placebo vs. 8 in the 0.3 mg/kg and 10 in the 0.6 mg/kd group No child had a side effect such that a decrease in medication dose or discontinuation in medication was required. Reduced appetite was noted for a substantial portion of the sample.	0 ; 0	NIMH, NIAAA, NIDA, NINDS, NIES, NICHHD	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Conners 1975 (Poor)	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 aggressive or 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)	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	Mean age=4.81 years Gender: 74.6% male Ethnicity: 100% white	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	59	3/0/56
Connor 2010 U.S.	Male and female subjects aged 6-12 years with a DSM diagnosis ADHD , a baseline score ≥24on ADHD rating scale 4 and a baseline score of ≥24 on the ADHD rating scale IV and a baseline score of ≥14 (males) and ≥12 (females) on the oppositional subscale of the Connor's parent rating scale revised: Long form were enrolled.	A. Guanfacine ER: 4mg/day B. Placebo Study period: 9 weeks	NR	Age, Mean (SD): 9.4 (1.84) yrs % Male: 68.7% % White: 66.4% % Black: 22.4% Hawaiian or other pacific islander: 0.5% American Indian or Alaska native: 2.8% Other: 7.9% Hispanic or Latino: 16.8%	ADHD subtype Inattentive: 12.6% Hyperactive: 3.3% Combined: 84.1% Mean (SD) oppositional subscale of CPRS-R:L score: 19.5 Mean ADHD-RS-IV total score: 42.3	217	60/5/unclear

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
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	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	In part by U.S. Public Health Service research grant # MH 18909 from the National Institute of Mental Health	
Connor 2010 U.S.	Guanfacine ER vs placebo Mean change from baseline in the oppositional subscale of the CPRS-R:L: -10.9 vs -6.8, p<0.001, effect size=0.59 LSM change from baseline in the oppositional subscale of the CPRS-R:L: 56.3% vs 33.4%, p<0.001 effect size: 0.64 LSM change from baseline in ADHD-RS total score: 23.8 vs 11.5, p<0.001, effect size: 0.92 LSM % reduction from baseline in ADHD-RS total score: 56.7% vs 26.5%, p<0.001, effect size:0.95	Guanfacine ER vs placebo % of patients with any AE: 84.6% vs 60.3% % of patients with TEAE: 83.8% vs 57.7% Somnolence: 50.7% vs 5.1% Headache: 22.1% vs 17.9% Sedation: 13.2% vs 1.3% Dizziness: 5.1% vs 3.8% Upper abdominal pain: 11.8% vs 2.6% Vomiting: 6.6% vs 6.4% Nausea: 2.9% vs 5.1% Fatigue: 11.0% vs 5.1% Irritability: 7.4% vs 2.6% Affect lability: 1.5% vs 5.1% Decreased diastolic blood pressure: 5.9% vs 1.3% Upper RTI: 2.9% vs 5.1% Pharyngolaryngeal pain: 2.9% vs 5.1%	Guanfacine ER vs placebo Total withdrawals: 21% vs 39.2% Withdrawals due to AE: 21% vs 1.3%	Shire Development Inc	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Corkum 2008 Canada	Stimulant medication-naive, meet DSM-IV criteria for one of the three ADHD subtypes, receive a recommendation to initiate a trial of MPH following the assessment, and have parents/caregivers who agreed to initiate a stimulant medication trial through the clinic pediatrician.	MPH and placebo were in identical capsules. 21 days; drug or placebo was administered at 8 a.m., 12 p.m., and 4 pm Children ≥25kg received 5 and 10mg doses Children >25kg received 10 and 15mg doses	NR	Mean age: 8.5 years (range: 6-12 years) 71.4% male	Learning disabilities: 6 (29%) Oppositional defiant disorder 2 (10%) Baseline scores CTRS - ADHD index: 71.10 CTRS - Inattention: 58.85 CTRS - Hyperactivity/Impulsivity: 67.90 CTRS - Oppositional: 62.55 CPRS - ADHD index: 68.90 CPRS - Inattention: 67.19 CPRS - Hyperactivity/Impulsivity: 65.43 CPRS - Oppositional: 61.00 11 (52.4%) had combined type 2 (9.5%) had hyperactive-impulsive type 8 (38.1%) had inattentive type	28/28/28	7/0/21

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Corkum 2008 Canada	Placebo vs Low dose vs Moderate dose Sleep diary at 3 weeks Time in bed: 585.97 vs 547.12 vs 547.56 (p<0.000 for placebo vs low dose and placebo vs moderate dose) Sleep onset latency: 24.71 vs 52.10 vs 51.14 (p<0.001 for placebo vs low dose and placebo vs moderate dose) Night awakenings: 0.16 vs 0.25 vs 0.23 (NS) Bedtime resistance: 29.42 vs 32.44 vs 30.13 (NS) Lights out: 21:13:05 vs 21:15:14 vs 21:15:02)NS) Sleep onset: 21:37:59 vs 22:02:45 vs 22:00:08 (p<0.002 for placebo vs low dose and placebo vs moderate dose) Sleep offset: 7:20:35 vs 7:15:57 vs 7:07:36 (NS) Sleep Disturbance Scale for Children at 3 weeks DIM: 57.71 vs 59.76 vs 62.05 SDB: 52.76 vs 53.71 vs 52.14 DA: 52.81 vs 51.00 vs 51.67 SWTD: 54.71 vs 57.14 vs 55.86 DOES: 53.86 vs 51.38 vs 52.24 SHY: 50.43 vs 50.43 vs 49.86 Total: 54.89 vs 55.40 vs 58.02 CTRS at 3 weeks ADHD Index: 67.40 vs 59.95 vs 59.65 (p<0.003 for placebo vs low dose and placebo vs moderate dose) Inattention: 57.00 vs 54.95 vs 52.85 (p<0.007 for placebo vs low dose and placebo vs moderate dose) Hyperactivity/impulsivity: 63.85 vs 57.45 vs 59.35 (p<0.01 for placebo vs low dose and placebo vs moderate dose) Oppositional: 59.25 vs 55.30 vs 55.15 (p<0.02 for placebo vs low dose and placebo vs moderate dose) CPRS at 3 weeks ADHD Index: 69.38 vs 63.05 vs 62.14 (p<0.005 for placebo vs low dose and placebo vs moderate dose) Inattention: 68.19 vs 62.86 vs 61.05 (p<0.007 for placebo vs low dose and placebo vs moderate dose) Hyperactivity/impulsivity: 64.00 vs 58.95 vs 59.67 (NS) Oppositional: 62.38 vs 55.57 vs 55.24 (NS)	NR	NR	IWK Health Centre in Halifax, Nova Scotia	Sleep is focus of study

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Dell'Agnello 2009 Italy	Patients of both sexes between 6-15 years, with ADHD and ODD diagnosed according to the DSM-IV criteria. Score of at least 1.5 SD above the age norm for the ADHD subscale of the SNAP -IV, a CGI-S ≥4 at both screening and baseline, a SNAP IV ODD subscale score of at least 15, and a normal intelligence i.e. a score of ≥70 on an IQ test	A. Atomoxetine target dose 1.2mg/kg/d (range 1.0 to 1.4mg/kg/d B. Placebo Treatment period: 1 wk screening , 6 weeks open label parent support phase, 8 weeks DB treatment phase	CYP2D6 inhibitors could be used only after consultation and permission of study staff physicians.	Mean age: 9.9 years Male: 92.9% Ethnicity: NR	Weight: 140.5cm Weight: 39.8 kg ADHD subtype Inattentive: 5.8% Hyperactive: 5.1% Combined: 89.1% Mean age at onset of ADHD symptoms: 4.1% Anxiety diagnoses from K-SADS GAD:10.9% Obsessive-compulsive disorder: 2.2% Panic disorder: 2.2% Separation anxiety disorder: 3.6% Specific phobias: 7.3% Affective diagnoses from K-SADS Adjustment disorder: 0.7% Dysthymia: 6.6% Major depressive disorder: 1.5% Seasonal pattern disorder: 1.5% Any other depressive disorders: 0.7%	139	5/0/137

Evidence Table 3. Data abstraction of placebo-controlled trials in children

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Dell'Agnello 2009 Italy	Atomoxetine vs placebo Mean (SD)change from baseline (visit 8-end of parent support phase)in the ADHD subscale score of SNAP-IV: -8.1 (9.2) vs -2.0 (4.7), p<0.001 between groups Mean (SD) change from baseline(visit 8-end of parent support phase) in the ODD subscale: -2.7 (4.1) vs -0.3 (2.6), p=0.001 between groups Proportion of patients with 25% improvement (reduction) in SNAP-IV ADHD subscale score: 39.0% vs 9.4%, p=0.001 Proportion of patients with 30% improvement (reduction) in SNAP-IV ADHD subscale score: 31.4% vs 6.3%, p=0.004 Proportion of patients with 40% improvement (reduction) in SNAP-IV ADHD subscale score: 18.1% vs 3.1%, p=0.043 Mean change from baseline (visit 8-end of parent support phase in CPRS-R:S subscales (p-values vs placebo) Oppositional: -1.2 vs 0.8 , p=0.002 Cognitive problems: -2.3 vs 0.2, p<0.001 Hyperactivity: -2.2 vs -0.7, p=0.022 ADHD index: -5.1 vs -0.1, p<0.001 Mean change from baseline (visit 8-end of parent support phase) in CTRS-R:S subscales(p values vs placebo) Oppositional: -1.1 vs 0.1, p=0.002 Cognitive problems: -3.8 vs 0, p=0.113 Hyperactivity: -2.1 vs -1.1, p=0.051 ADHD index: -3.5 vs -1.5, p=0.061 Mean change from baseline (visit 8-end of parent support phase) in CGI-ADHD-S score: -0.6 vs 0.1, p<0.001 Mean change in CDRS total score (visit 8-end of parent support phase)-0.5 (4.4) vs -0.1 (5.5), p=0.870 between groups Mean change from baseline (visit 8-end of parent support phase) in SCARED: -2.1 (7.6) vs -1.7(6.5), p=0.836	Atomoxetine vs placebo Anorexia: 33.6% vs 9.4%, p=0.006 Somnolence: 29.9% vs 6.3%, p=0.004 Headache: 21.5% vs 12.5%, p=0.316 Nausea: 20.6% vs 0.0%, p=0.002 Abdominal pain: 15.0% vs 6.3%, p0.245 Vomiting: 14.0% vs 3.1%, p=0.118 Abdominal pain upper: 10.3% vs 12.5%, p=0.748	Atomoxetine vs placebo (DB phase) Total withdrawals : 5 vs 0 Withdrawals due to AE: 3 vs 0	Eli Lilly, Italy	There were 17 withdrawals before randomization during parent support phase

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Dittman 2011 Germany	Patients aged 6-17, meeting DSM-IV-TR criteria for ADHD (any subtype) and DSM-IV-TR criteria A-C of ODD.	A. Atomoxetine 0.5mg/Kg QD for 7 days, followed by target dose 1.2mg/Kg B. Atomoxetine 0.5mg/Kg QD for 7 days, followed by 0.8mg/Kg for 7 days followed by target dose of 1.2mg/Kg C. Placebo Treatment period: 9 weeks	No concomitant psychotropic medications allowed	Mean age: 11 years Male: 84.4% Ethnicity: NR	BMI: 19.1 mg/m^2 ADHD combined: 75.6% Predominantly inattentive: 19.5% Predominantly hyperactive-impulsive: 5% ODD diagnosis: 74.4% CD diagnosis: 24.4% Previous stimulant exposure: 44.4% Mean SNAP-IV ADHD score: 37.3 Mean SNAP-IV ADHD inattention score: 17.8 Mean SNAP-IV ADHD hyperactivity-impulsivity score: 19.5 Mean SNAP-IV ODD score: 15.5 Mean CGI-S ADHD score:5.1 Mean CGI-S ODD score: 5.0	181	52/0/180

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Dittman 2011 Germany	SNAP-IV ODD score, LS mean treatment group difference at wk 9, atomoxetine pooled minus placebo (95% CI): -3.2(-5.0 to -1.5), effect size -0.69, p<0.001 Atomoxetine fast vs atomoxetine slow vs placebo Decrease in ODD symptom severity at wk 9, LS mean, 95% CI: 8.6 (7.2 to 9.9) vs 9.0 (7.7 to 10.3) vs 12.0 (10.6 to 13.5), atomoxetine fast vs placebo: effect size -0.74, p<0.001, atomoxetine slow vs placebo effect size -0.65, p=0.003, fast vs slow: effect size -0.09, p=0.669 % of patients with 30% and at least 50% improvement in SNAP IV ODD subscale score: 48.3% and 35.0% vs 55.7% and 47.5% vs 35.6% and 16.9% SNAP-IV ADHD score , LS mean treatment group difference at wk 9, atomoxetine pooled minus placebo (95% CI): -7.4 (-11.0 to -3.8), effect size-0.72, p<0.001 Decrease in ADHD severity at wk 9, LS mean 95% CI: 22.9 (20.1 to 25.8) vs 21.3 (18.5 to 24.1) vs 29.6 (26.6 to 32.5) atomoxetine fast vs placebo effect size 0.002 , p=0.002, atomoxetine slow vs placebo effect size -0.80, p<0.001, atomoxetine fast vs slow effect size -0.16, p=0.416 ADDB-Inv disruptive behavior disorder score, LS mean treatment group difference at wk 9 atomoxetine pooled minus placebo , 95% CI: -1.4 (-2.1 to -0.7), effect size=-0.62 , p<0.001, atomoxetine fast vs placebo effect size -0.66, p<0.001, atomoxetine slow vs placebo effect size-0.57, p=0.002 fast vs slow effect size -0.09, p=0.607 At wk 9 LS mean treatment group difference atomoxetine pooled minus placebo, 95% CI Individual target behavior intensity: -3.5 (-6.2 to -0.9) effect size -0.52, p=0.01 Individual target behavior frequency: -1.8 (-3.2 to-0.4), effect size -0.53, p=0.01 CGI-ODD score:-0.8 (-1.1 to -0.4) effect size -0.22, p<0.001 CGI-ODD+ADHD: -0.7 (-1.1 to -0.4) effect size 0.21, p<0.001, each titration group for CGI superior to placebo (p<0.01), atomoxetine fast vs slow p=NS	Atomoxetine fast vs slow vs placebo Proportion of patients with any treatment related AE: 70% vs 57.4% vs 30.5% Proportion of patients with SAE: 1.7% vs 1.6% vs 1.7% Proportion of patients with any clinically relevant adverse drug reactions: 60.0% vs 44.3% vs 18.6, fast vs placebo p<0.001, slow vs placebo p=0.003, fast vs slow p=0.102 Fatigue: 35.0% vs 21.3% vs 10.2% Clinically relevant fatigue or related symptoms: 31.7% vs 23.0% vs 10.2%, fast vs placebo p=0.006 , slow vs placebo p=0.086, fast vs slow p=0.313 Nausea: 21.7% vs 19.7% vs 5.1% Clinically relevant nausea or related symptoms: 35.0% vs 29.5% vs 8.5%, fast vs placebo p=0.001, slow vs placebo p=0.005, fast vs slow p=0.563 Headache: 25.0% vs 14.8% vs 15.3% Vomiting: 15.0% vs 18.0% vs 5.1% Upper abdominal pain: 15.0% vs 13.1% vs 0.0% Anorexia: 15.0% vs 11.5% vs 1.7% Clinically relevant GI complaints: 20.0% vs 13.1% vs 3.4%, fast vs placebo p=0.008, slow vs placebo p=0.095, fast vs slow: p=0.338	Atomoxetine fast vs slow vs placebo Total withdrawals: 26.7% vs 21.3% vs 37.3% Withdrawals due to AE: 10% vs 3.3% vs 1.7% Time to early drop out HR, 95% CI Patients on atomoxetine slow group stayed on treatment longer than placebo: 3.57 (1.42 to 8.94), p=0.007 Atomoxetine slow vs placebo: 1.57 (0.78 to 3.19), p=0.208 Atomoxetine fast vs slow group: 2.24 (0.85 to 5.89), p=0.103	Lilly Deutschland GmbH, Bad Homburg, Germany	

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Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Findling 2011 U.S.	Patients 13-17 years who met DSM-IV-TR criteria for ADHD. ADHD diagnosis was confirmed using K-SADS-PL, moderate to severe ADHD symptoms at baseline (score of ≥28 on the ADHD rating scale IV : Clinician version, age appropriate intellectual function and blood pressure measurements ≤95th percentile for age, gender and height.	Lisdexamfetamine A.30mg/d B. 50mg/D C. 70mg/d D. Placebo Time period: 4 weeks	Stable dose of thyroid medication for at least 3 mo was permitted.	Mean (SD) Age: 14.6 (1.31) Female: 29.7% White: 79% African American: 14.8% Hispanic/Latino: 14.8%	Mean ADHD-RS-IV total score: 37.8 (SD 6.88) % of patients moderately or markedly ill: 95.2% by CGI-S Mean baseline CGI-S score: 4.5 Combined ADHD subtype:67.6%	314	49/6/309

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Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Findling 2011 U.S.	Lisdexamfetamine 30mg vs 50mg vs 70mg vs placebo (p-values are vs placebo) Placebo adjusted ADHD-RS-IV total score LS mean (95% CI) : 30mg -5.5 (-9.7 to -1.3) vs 50mg -8.3 (-12.5 to -4.1) vs 70mg -7.9 (-12.1 to -3.8), p≤0.056 for each. At endpoint, the adjusted LS mean (SE)change(improvement) from baseline in ADHD-RS-IV total score: -18.3 (1.25) vs -21.1 (1.28) vs -20.7 (1.25) vs -12.8 (1.25) Proportion of patients reporting "improved" on CGI-I: 57.9% vs 73.6% vs 76.0% vs 39.5%, p≤0.0001 (for all lisdexamfetamine groups combined vs placebo) Mean change from baseline in YQOL-R total scores: 1.8 vs 0.8 vs 0.8 vs 1.8, p=NS Mean change(SE) from baseline in SBP, mmHg: -0.8(1.22) vs 0.3 (1.01) vs 1.7 (1.21) vs 2.2 (1.04) Mean change (SE) from baseline in DBP, mmHg: -0.5 (1.05) vs 0.4 (0.84) vs 3.4 (0.80) vs 0.5 (0.97) Mean change from baseline in pulse rate, bpm: 5.0 (1.18) vs 3.8 (1.37) vs 5.4(1.27) vs 0.8 (1.36)	Lisdexamfetamine 30mg vs 50mg vs 70mg vs placebo Proportion of patients with any TEAE: 65.4% vs 68.8% vs 71.8% vs 58.4% Proportion of patients with severe TEAE (all lisdexamfetamine groups vs placebo): 1.7% vs 2.5% Decreased appetite: 37.2% vs 27.3% vs 37.2% vs 2.6% Dizziness: 1.3% vs 5.2% vs 6.4% vs 3.9% Fatigue: 5.1% vs 2.6% vs 5.1% vs 2.6% Headache: 11.5% vs 16.9% vs 15.4% vs 13.0% Insomnia: 9.0% vs 10.4% vs 14.1% vs 3.9% Irritability: 7.7% vs 2.6% vs 10.3% vs 3.9% Nausea: 1.3% vs 3.9% vs 6.4% vs 2.6% URTI: 2.6% vs 5.2% vs 5.1% vs 7.8% Vomiting: 0% vs 1.3% vs 2.6% vs 5.2% Weight increased: 3.8% vs 9.1% vs 15.4% vs 0% Mean changes in weight from baseline(lb) -3.0 vs -4.5 vs -5.2 vs 2.3 Weight increase≥7% (all lisdexamfetamine groups vs placebo): 0% vs 1.5% Weight decrease≥7%: (all lisdexamfetamine groups vs placebo): 4.7% vs 0%	Lisdexamfetamine(all groups combined) vs placebo Total withdrawals:16.6% vs 12.7% Withdrawals due to AE:4.3% vs 1.3%	Shire Development Inc	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Findling 2007 U.S.	Youths ages 5-17 years, meeting DSM IV criteria for a diagnosis of a bipolar spectrum disorder and a comorbid diagnosis of ADHD and the use of a psychostimulant was clinically indicated for the treatment of dysfunctional residual symptoms of ADHD. Patients were required to be treated with fixed doses of mood stabilizers at the time of study enrollment for at least 5 days before receiving study medication.	MPH twice a day (morning and midday): either 5mg, 10mg, or 15mg Placebo	Mood stabilizers required Lithium and Divalproex sodium allowed	Mean age: 10.43 years 75% male 75% Caucasian 19% Hispanic 6% African American	Bipolar I disorder: 88% Bipolar II disorder: 6% Bipolar disorder not otherwise specified: 6% ADHD combined type: 94% ADHD inattentive type: 6% ADHD hyperactivity/impulsivity type: 0%	NR/NR/20	4/0/16

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Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Findling 2007 U.S.	**Placebo vs 5 mg vs 10 mg vs 15 mg vs Best Dose Week** ARS-IV Inattentive: 17.81 vs 15.94 vs 13.87 vs 10.88 vs 11.25 (p<0.05 for 10mg and 15mg vs baseline and for best dose week vs placebo) ARS-IV Impulsivity/Hyperactivity: 14.38 vs 14.25 vs 12.47 vs 8.94 vs 9.56 (p<0.05 for 10mg and 15mg vs baseline and for best dose week vs placebo) ARS-IV local scores: 32.19 vs 30.19 vs 26.33 vs 19.81 vs 20.81 (p<0.05 for 10mg and 15mg vs baseline and for best dose week vs placebo) CPRS-48 Conduct Problem subscale T score: 73.9 vs 71.9 vs 60.2 vs 56.0 vs 62.8 (p<0.05 for 10mg and 15mg vs baseline and for best dose week vs placebo) CPRS-48 Learning Problem subscale T score: 77.0 vs 75.0 vs 64.2 vs 60.0 vs 65.3 (p<0.05 for 10mg and 15mg vs baseline and 15mg vs placebo) CPRS-48 Impulsive-Hyperactive subscale T score: 64.0 vs 64.5 vs 53.1 vs 54.0 vs 54.2 (p<0.05 for 10mg and 15mg vs baseline and for best dose week vs placebo) CPRS-48 Hyperactivity Index subscale T score: 73.1 vs 69.8 vs 57.3 vs 55.8 vs 59.2 (p<0.05 for 10mg vs baseline and for 15mg and best dose week vs placebo) CGI-Severity: 3.50 vs 3.07 vs 2.69 vs 2.19 vs 2.50 (p<0.05 for 5mg and 10mg vs baseline and for 15mg and best dose week vs placebo) YMRS: 3.03 vs 3.56 vs 2.44 vs 1.25 vs 0.94 (NS) CDRS-R: 18.19 vs 18.31 vs 17.75 vs 17.75 vs 17.69 (NS)	**Placebo vs 5 mg vs 10 mg vs 15 mg vs Best Dose Week** Insomnia or trouble sleeping: 2 vs 1 vs 2 vs 5 vs 0 Stares or daydreams: 2 vs 1 vs 1 vs 2 vs 1 Talks less with others: 2 vs 0 vs 0 vs 0 Uninterested in others: 1 vs 2 vs 0 vs 0 vs 0 Decreased appetite: 1 vs 4 vs 4 vs 5 vs 4 Irritable: 6 vs 5 vs 3 vs 3 vs 0 Stomachaches: 1 vs 2 vs 4 vs 3 vs 1 Headaches: 0 vs 0 vs 1 vs 0 vs 0 Drowsiness: 4 vs 3 vs 0 vs 0 vs 1 Sad/unhappy: 1 vs 2 vs 1 vs 1 vs 0 Prone to crying: 0 1 vs 1 vs 0 vs 1 Anxious/worried: 3 vs 2 vs 1 vs 3 vs 1 Perseveration verbal/behavior: 2 vs 0 vs 0 vs 0 vs 0 Bites fingernails: 2 vs 3 vs 4 vs 3 vs 4 Euphoric/unusually happy: 1 vs 1 vs 0 1 vs 0 Dizziness: 0 vs 0 vs 0 vs 1 vs 0 Tics or nervous movements: 0 vs 0 vs 2 vs 2 vs 2 Over focused: 0 vs 3 vs 2 vs 2 vs 1 Rebound effects: 1 vs 3 vs 5 vs 4 vs 3	4 withdrawals 2 due to AEs	Many authors have financial ties to pharmaceutical companies, but no direct funding was given from pharmaceutical companies to this study	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Gadow 2008 U.S.	Potential subjects had to meet DSM-III-R (American Psychiatric Association, 1987) or DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for ADHD and either chronic motor tic disorder or Tourette's syndrome.	MPH and placebo given in identical pills 3 dosage regimes of MPH by weight: 0.1mg/kg (mean 4.5mg) 0.3mg/kg (mean 9.3mg) 0.5mg/kg (mean 14.3mg) Maximum dose: 20mg	NR	Mean age: 8.95 years 80% male 87% European 6% Hispanic 6% African 1% Asian	Mean age at tic onset: 5.6 years Receiving special education full time: 27% Receiving special education part time: 31% Not receiving special education: 42%	NR/NR/71	NR

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Gadow 2008 U.S.	Placebo vs 01.mg/kg MPH vs 0.3mg/kg MPH vs 0.5mg/kg MPH Teacher Ratings ATRS: 11.6 vs 8.0 vs 7.3 vs 5.7 (p=0.0001 for all doses compared to placebo) Factor 1: 9.3 vs 6.5 vs 5.9 vs 4.6 (p=0.0001 for all doses compared to placebo) Factor 2: 2.2 vs 1.5 vs 1.6 vs 1.1 (p=0.0001 for all doses compared to placebo) IOWA Conners I-O Scale: 7.4 vs 5.2 vs 4.7 vs 3.8 (p=0.0001 for all doses compared to placebo) O/D Scale: 3.4 vs 1.9 vs 1.7 vs 1.1 (p=0.0001 for all doses compared to placebo) Peer Conflict Scale: 3.7 vs 2.0 vs 1.6 vs 1.1 (p=0.0001 for all doses compared to placebo) Parent ratings APRS: 11.0 vs 8.2 vs 10.0 vs 7.8 (p=0.0249 for all doses compared to placebo) Factor 1: 7.3 vs 5.4 vs 5.1 vs 4.3 (p=0.0001 for all doses compared to placebo) Factor 2: 3.4 vs 2.7 vs 2.9 vs 2.5 (p=0.0721 for all doses compared to placebo) MOMS Hyperactivity scale: 2.9 vs 2.3 vs 2.3 vs 1.7 (p=0.0001 for all doses compared to placebo) Aggression scale: 2.1 vs 1.4 vs 1.6 vs 1.3 (p=0.0003 for all doses compared to placebo) Peer Conflict Scale: 4.6 vs 3.2 vs 3.2 vs 2.5 (p=0.0001 for all doses compared to placebo) CPT Inattention: 7.3 vs 6.0 vs 5.1 vs 5.1 (p=0.0010 for all doses compared to placebo) Impulsivity: 3.1 vs 3.2 vs 1.8 vs 2.4 (p=0.0001 for all doses compared to placebo) Dyscontrol: 6.5 vs 7.3 vs 2.7 vs 3.6 (p=0.0001 for all doses compared to placebo) Clinic Classroom On-task: 79.8 vs 85.8 vs 90.5 vs 89.8 (p=0.0001 for all doses compared to placebo) Fidgets: 22.8 vs 20.8 vs 18.4 vs 16.9 (p=0.0064 for all doses compared to placebo) Worksheet items: 242 vs 281 vs 281 vs 285 (p=0.0001 for all doses compared to placebo) Physician ratings YGTSS - total motor: 12.7 vs 12.8 vs 12.7 vs 12.8 vs (NS) YGTSS - total phonic: 8.5 vs 7.7 vs 8.1 vs 8.7 (NS) YGTSS - Impairment: 10.7 vs 9.7 vs 11.5 vs 10.4 (NS) YGTSS - Global Severity: 31.8 vs 30.3 vs 32.2 vs 30.5 (NS) Shapiro TSSS: 2.0 vs 1.9 vs 1.9 vs 1.9 (NS) GTRS - Motor: 5.0 vs 5.1 vs 5.0 vs 5.1 (NS) GTRS - Vocal: 1.3 vs 1.2 vs 1.3 vs 1.3 (NS) GTRS - Total: 3.1 vs 1.1 vs 2.8 vs 2.4 (NS)	Placebo vs 0.1mg/kg MPH vs 0.3mg/kg MPH vs 0.5mg/kg MPH Teacher SSEC Mood index: 3.5 vs 2.7 vs 2.6 vs 2.6 (p=0.0047) Attention/arousal index: 1.8 vs 1.5 vs 1.5 vs 1.2 (p=0.0021) Somatic index: 0.4 vs 0.3 vs 0.4 vs 0.5 (NS) Motor movements: 1.1 vs 0.7 vs 0.8 vs 0.7 (p=0.0110) Parent SSEC Mood index: 2.1 vs 1.8 vs 1.9 vs 1.9 (NS) Attention/arousal index: 0.6 vs 0.8 vs 0.8 vs 0.9 (NS) Somatic index: 1.1 vs 1.5 vs 1.8 vs 2.0 (p=0.0001) Motor movements: 1.2 vs 1.0 vs 1.0 vs 0.8 (p=0.0572) Cardiovascular Systolic: 99.0 vs 100.6 vs 102.3 vs 104.3 (p=0.0999) Diastolic: 60.0 vs 61.4 vs 61.0 vs 64.5 (p=0.0386) Heart rate: 86.0 vs 88.8 vs 91.7 vs 91.6 (p=0.0326) Weight: 79.3 vs 78.3 vs 78.1 vs 77.8 (p=0.0040)	NR	None	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Gadow 1992	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.	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.	NR	Mean age=8.3(1.96), range 6.1-11.9 years. Gender=11(100%) male Race: NR	Overall Impairment Rating scores from the Yale Global Tic Severity Scale: 2(18.2%): none 4(36.4%): minimal 4(36.4%): mild 1(9.1%): severe Global Severity Scores: mean=40.6(16.6), range 16-79 ADHD index: mean=8.7(1.77) Conners Hyperactivity index: mean=17.6(3.53) PSSC Hyperactivity subscale: mean=4.2(1.25) Comorbidities: 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%)	11	0/0/0

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
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. Motor: 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)	NS in SSEC * no other side effect information	none	Tourette Syndrome Association and NIMH grants; CIBA supplied MPH and placebo	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Gadow 1995	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	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 0.5mg/kg dose was 20mg.	NR	Mean age=8.8(1.9), range 6.1-11.9 years. Gender=31(91.2%) male Race: NR	100% ADHD and either chronic motor tic disorder or Tourette disorder Tourette disorder: definite=22(64.7%), by history=12(35.3%)	34	0/0/34
Gadow 2011 U.S.	Children aged 6-12 years meeting DSM III-R criteria or DSM IV diagnostic criteria for ADHD and either CMTD or Tourette's disorder according to research diagnostic criteria.	Mean dose A. Methylphenidate IR 4.7 mg (SD 1.4) B. Methylphenidate IR 9.5 mg (SD 2.8) C. Methylphenidate IR 14.5mg (SD 3.0) Treatment period: 8 weeks	NR	Age: 9.1 years Male: 77.8% Caucasian: 90.7%	Age tic onset: 5.8 Socioeconomic status: 36.6 Parent ratings: Conners Hyperkinesis Index: 17.1 Teacher ratings: Conners Hyperkinesis index: 17.3 IOWA Conners I-O scale: 10.6 YGTSS global severity score: 35.2	54	NR/NR/NR

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Gadow 1995	Placebo vs. 0.1mg/kg; Placebo vs. 0.3mg/kg; Placebo vs. 0.5mg/kg; 0.1mg/kg vs. 0.5mg/kg Classroom observation-- a. Interference: p<0.05; p<0.05; p<0.01; p<0.05 b. Moter: p<0.05; p<0.01; p<0.01; p<0.05 c. Off-task: p<0.01; p<0.01; p<0.01; p<0.01 d. Noncompliance: p<0.01; p<0.01; p<0.01; p<0.05 e. Nonphysical aggression: NS; NS; NS; NS Lunchroom observation-- a. Noncompliance: NS; p<0.05; p<0.01; NS b. Physical aggression: NS; NS; p<0.01; NS c. Nonphysical aggression: NS; p<0.01; <0.05; NS Playground observation: a. Nonphysical aggression: p<0.01; p<0.05; p<0.05; NS School tic observations: a. Motor tic observation: p<0.05; NS; NS; NS Minimal effective dose: mean=0.29mg/kg/bid or 8.8mg (range 2.5mg-20mg)	NR	none	Tourette Syndrome Association and NIMH grants; CIBA supplied MPH and placebo	
Gadow 2011 U.S.	Treatment response in ADHD +anxiety group Placebo vs Methylphenidate IR 0.1mg/kg vs 0.3mg/kg vs 0.5mg/kg ATRS, mean, (SD): 10.9 (8.1) vs 7.3 (5.1) vs 9.2 (5.9) vs 5.9 (5.3) IOWA Conners I-O scale mean (SD): 6.7(4.7) vs 4.4 (3.3) vs 5.9 (3.7) vs 3.8 (3.1), F ratio 5.31, p=0.0030 IOWA Conners O-D scale mean (SD): 4.2 (3.8) vs 1.9 (2.3) vs 2.6 (3.0) vs 1.6 (2.1), F ratio 5.00, p, p=0.0043 APRS mean (SD): 11.5 (7.7) vs 9.3 (6.4) vs 8.6 (5.2) vs 8.6 (5.6), F ratio 2.08, p=0.1151	Teacher-rated SSEC mood index F=2.96 p<0.04, post hoc comparison placebo vs 0.5mg/Kg indicated larger treatment effect in the ADHD+Anxiety group (ES=0.44) than ADHD-Anxiety group (ES=0.35) Systolic blood pressure (F=3.37, p=0.3) post-hoc comparison indicated significant methylphenidate induced increase for 0.5mg/Kg dose (Mean=107.7, SD 16.1) over placebo (mean 93.4, SD 23.3) in ADHD+Anxiety group. ADHD-anxiety group p=0.70	NR; NR	Tourette Syndrome Association Inc and P.H.. Grant no. MH 45358 from National Institute of Mental Health	

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Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Gau 2007	Taiwanese children and adolescents aged 6-16 years; met DSM-IV criteria for diagnosis of ADHD, confirmed by Chinese version of K-SADS-E; ADHD-RS-IV-Parent Version: Investigator Administered and Scored Total Score of at least 25 for boys and 22 for girls, or greater than 12 for their diagnostic subtype at both visit 1 and visit 2; normal intelligence; no ADHD medication or completion of the washout procedures	Study period I: Medication-free screening/assessment Study period II: Atomoxetine 1.4 mg/kg QD (mean final dose) vs placebo x 6 weeks	Concomitant use of other psychoactive medications not allowed	Mean age=9.2 years 89% male 100% Taiwanese	Height (cm): 133.6 Weight (kg): 31.5 Previous psychostimulants (# pts): 57.5% Family ADHD history: 15.1% ADHD Subtype Combined: 73% Inattentive: 27% Comorbid conditions ODD: 16% Conduct Disorder: 8.5% ADHD-RS-IV, total score: 36.8 points CGI-ADHD-S: 5.3 CPRS-R:S, total score: 44 CTRS-R:S, total score: 30.6	106	8 (7.5%) withdrawn/lost to FU NR/98 (92%) analyzed
Geller 2007	Children and adolescents ages 8 to 17 years who met DSM-IV criteria for ADHD and for at least one of the following anxiety disorders: separation anxiety disorder, generalized anxiety disorder or social phobia; at visits 2 and 3, patients must have had a total or subscale score on the ADHD-RS-IV-PI of at least 1.5 SDs above age and sex norms for ADHD subtype, and a total score on the Pediatric Anxiety Rating Scale (PARS) of at least 15 (max score=25); ADHD diagnoses were confirmed clinically, and anxiety and ADHD	Study period I: Single-blind placebo run-in x 2 weeks Study period II: Atomoxetine 1.3 mg/kg/day (mean final dose) or placebo x 12 weeks	NR	Mean age= 12 years 64.8% male 80.7% white	Prior stimulant exposure: 62% ADHD subtype Combined: 75% Inattentive: 24% Hyperactive/Impulsive: 1% Height (mean cm): 150.1 Weight (mean kg): 46.8 Separation anxiety disorder, generalized anxiety disorder or social phobia	176	44 (25%)/1 (0.5%)/176 (100%)

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Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Gau 2007	**Atomoxetine vs placebo: Mean change scores** ADHD-RS-IV Total Score: -17.3 vs -9.3, p=0.002 CGI-ADHD-S: -2 vs -1; p<0.001 CPRS-R:S Total Score: -12.8 vs -3.5; p<0.001 CTRS-R:S Total Score: -6.8 vs +0.8; p=0.028 Oppositional subscale: -0.1 vs +0.1; NS	**Atomoxetine vs placebo** Decreased appetite: 26 (36.1%) vs 5 (17.4%); p=0.02 Somnolence: 16 (22.2%) vs 3 (8.8%); NS Nausea: 12 (16.6%) vs 0; p<0.01 Cough Increased: 9 (12.5%) vs 7 (20.6%); NS Insomnia: 8 (11.1%) vs 1 (2.9%); NS Headache: 7 (9.7%) vs 2 (5.9%); NS Dizziness: 7 (9.7%) vs 1 (2.9%); NS Asthenia: 7 (9.7%) vs 0; p=0.09 Rhinitis: 6 (8.3%) vs 0; NS Abdominal pain: 6 (8.3%) vs 0; NS Pharyngitis: 5 (6.9%) vs 3 (8.8%); NS Vomiting: 5 (6.9%) vs 3 (8.8%); NS Diarrhea: 4 (5.6%) vs 0; NS Weight loss: 4 (5.6%) vs 0; NS Fever: 3 (4.2%) vs 5 (14.7%); NS	Total withdrawals: NR separated by group Withdrawals due to AE's: 1 (1.4%) vs 0; NS	Eli Lilly & Company	
Geller 2007	Lisdexamfetamine vs placebo Mean change from baseline ADHD-RS-IV-PI: -9 vs -0.7, p<0.001 PARS: -4.5 vs -2.4, p<0.01 CGI-S: -0.9 vs -0.4; p=0.002 MASC: -4.6 vs 2.1; p=0.009 LPS-ADHD-R: 9.5 vs 3.1; p=0.002 CHQ-PF50: 6.9 vs 3.3; 0.019	Mean weight loss (kg): -0.55 vs +1.39; p<.001 Decreased appetite: 11 (14.3%) vs 3 (3.8%); p=0.025 Headache: 11 (14.3%) vs 7 (8.8%), NS Upper abdominal pain: 9 (11.7%) vs 4 (5%), NS Vomiting: 8 (10.4%) vs 4 (5%), NS Irritability: 5 (6.5%) vs 3 (3.8%), NS Nasopharyngitis: 5 (6.5%) vs 5 (6.3%), NS Nausea: 5 (6.5%) vs 2 (2.5%), NS Cough: 4 (5.2%) vs 5 (6.3%), NS Influenza: 4 (5.2%) vs 1 (1.3%), NS Sinusitis: 4 (5.2%) vs 3 (3.8%), NS	Overall withdrawals: 12 (15%) vs 14 (16%) Withdrawals due to AE's: 1 (1%) vs 1 (1%)	Eli Lilly & Company	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Gonzales-Heydrich 2010 U.S.	Confirmed epilepsy diagnosis according to International League Against Epilepsy's International Classification of Epilepsy Seizures, diagnosis of ADHD and its subtype according to DSM-IV-R criteria, stable regimens of antiepileptic drugs, at least one seizure within the past 5 yrs, freedom from seizure for 1 mo prior to starting study medication, CGI-ADHD-S<4, ADHD-IV home version was above 90th percentile on the inattentive, hyperactive-Impulsive and total score	A. Start dose methylphenidate IR 5 mg-max dose OROS methylphenidate 18mg B. Start dose methylphenidate IR 5mg- max dose OROS methylphenidate 36mg C. Start dose methylphenidate IR 5mg-max dose OROS methylphenidate 54mg D. Placebo Treatment period=crossover trial, 1 wk for group A, 2 weeks for group B. 3 weeks for Group C	A stable regimen of antiepileptic drugs(valproate, carbamazepine, lamotrigine, topiramate, Levetiracetam, Gabapentin, Oxcarbazepine, Ethosuximide, Lorazepam, Diazepam)	Mean (SD) Age: 10.5 (3.0) Median 10.4, range 6.4-17.5 Male: 57.6%	Mean (SD)Weight, kg: 42.4 (16.3), median 37.7, range (20.9-84.4) Mean (SD)WASI, IQ: 89.7 (16.9), median 88, range (59-123) Mean (SD) Antiepileptic drugs at start: 1.2, median 1.2 (0.5) median 1, range (1-3) Epilepsy etiology Cryptogenic: 36.4% Idiopathic: 39.4% Symptomatic: 24.2% Seizure type Focal onset: 78.8% Generalized onset: 21.2% ADHD subtypes Predominantly inattentive: 48.5% Combined: 51.1%	33	19/NR/33

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Gonzales-Heydrich 2010 U.S.	Proportion of respondents (data from graph) 18mg methylphenidate vs placebo: 45% vs 5% 36mg methylphenidate vs placebo: 48% vs 9% 54 mg methylphenidate vs placebo: 65% vs 0% Change from baseline in ADHD rating scale score by dose (data from graph) p<0.02 vs placebo for all methylphenidate groups Placebo vs 18 mg (at wk 1): -1vs -7 Placebo vs 36 mg (wk 2): -2 vs -8 Placebo vs 54 mg (wk 3): -2 vs -12 No. of patients experiencing seizure: 4 methylphenidate vs 3 placebo, p=NS	Methylphenidate vs placebo Methylphenidate vs placebo Emotional lability: 4 vs 2 Trouble falling asleep: More likely in methylphenidate group vs placebo $x^2$10.60, p=0.01	Total withdrawals:14 vs 5 Withdrawals due to AE: NR	NIMH Grant K23 MH066835	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Gorman 2006	Ages 6 to 12; WISC-III Full Scale IQ ≥80. To confirm the diagnosis of ADHD, ≥6 inattention and/or hyperactivity/impulsivity symptoms on the Parent Interview for Child Symptoms-4, a semistructured DSM interview administered by the second author and ≥4 symptoms of inattention and/or ≥4 symptoms of hyperactivity/impulsivity on the teacher ADHD scale, a Likert scale comprising of 18 DSM-IV symptoms for ADHD were required. The count of inattention or hyperactivity/impulsivity symptoms endorsed by the parent was supplemented by up to two ADHD symptoms for each symptom cluster reported by the teacher.	Methylphenidate: Mean Dose: 33.1 mg/day Dose Range: Terminal daily doses from 25 to 50 mg	none/NR	Mean age: 9.1 yrs (Range: 6 to 12 yrs) Male: 52% Ethnicity: 91% Caucasian	**Frequency or mean** Socioeconomic status: 50.60, NS Anxiety disorders:7 lifetime affective disorder: 2 ODD:18, p<0.001 Wechsler full-scale IQ: 113.86, p<0.001 Basic Reading Skills Index: 113.44, p<0.001 Broad Mathematics Index: 115.98, p<0.001 Kaufman Test of Academic Achievement, Spelling: 107.91, p<0.001 ADHD subtypes: mixed: 22 (29.3%), inattentive: 19 (25.3%), control group 34 (45.3%)	75	NR/NR/NR

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Gorman 2006	Mean change from pretrial (+/- SD) Parent ratings [placebo or matched session vs. MPH or matched session] / teacher ratings [placebo or matched session vs. MPH or matched session] **Inattention/Overactivity** Controls: 0.13(0.09) ADHD/I: -0.08 vs. -0.40 / -0.13 vs. -0.67, p<0.05 ADHD/C: -0.17 vs. -1.06 / -0.08 vs -0.94, p<0.001 **Hyperactivity** Controls: -.98(.06) ADHD/I: 0.05 vs. 0.12 / 0.08 vs. -0.13, p<0.05 ADHD/C: -0.04 vs. -0.44 / 0.11 vs -0.45, p<0.001 **Attention** Controls: .72(.06) ADHD/I: -.07 vs 0.21 / -0.17 vs 0.21, p<0.05 ADHD/C: 0.10 vs 0.49 / -0.07 vs. 0.46, p<0.001 **Aggression/Oppositionality** Controls: .25(.09) ADHD/I: 0.05 vs -0.03 / -0.10 vs -0.22, NS ADHD/C: 0.25 vs -0.47 / -0.10 vs. -0.58, p<0.001 **Aggression** Controls: .21(.06) ADHD/I: 0.03 vs 0.01 / 0.05 vs 0.04, NS ADHD/C: 0.15 vs -0.16 / -0.06 vs -0.27, p<0.001 **Valence of interview responses/comments,** ADHD/I: 0.26(.32) vs 1.10(.37) / -0.76(.42) vs 0.50(.43) ADHD/C: -0.15(.30) vs 1.80(.34) / -0.96(.39) vs 0.97(.40)	MPH vs. Placebo, mean of body weight and counts of side effects (+/-SE) Body Weight (Kg): 36.09(1.99) vs. 36.54(2.01), p=0.18 Somatic Complaints: 1.14(.15) vs. 0.29(.10), p=0.001 Behavioral Complaints: 1.18(.19) vs. 1.30(.21), NS	NR/NR	NIMH grant # MH56571	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Greenhill 2002	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 ADHD, 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.	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.	No	Mean age =9 years Male=81.8% White = 81.4% African American = 15.3% Hispanic = 10.2% Other = 3.5%	Previously treated for ADHD = 64 .0%(n=201) Mean Conners' Global Index - Teacher = 12.1 Mean Conners' Global Index - Parent = 13.2 Mean CGI Severity of Disorder = 4.45	321	45 withdrawn (n=28 from placebo, n=17 from MPH MR) /NR /314 analyzed (n=155 MPH MR; n=159 placebo)

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Greenhill 2002	At endpoint, investigators rated 64% of children as moderately or markedly improved with MPH MR treatment, compared with 27% of the placebo group. Conners' Global Index - Teacher's Scores (MPH MR vs. placebo): Baseline mean (Standard deviation): 12.7 (7.2) vs. 11.5 (7.35) (p=0.1309) Week 1 mean (SD): 7.3 (4.93) vs. 10.9 (6.56) (p=0.0001) Week 2 mean (SD): 5.8 (4.71) vs. 10.4 (6.75) (p=0.0001) Week 3 mean (SD): 4.7 (4.77) vs. 9.2 (6.30) (p=0.0001) Least squares 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.	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 occurring at an incidence >=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, no erythematous, periumbilical rash on the 6th day of MPH MR treatment; whereas the other children developed a headache on Day 4 and dizziness + stomachache on Day 5 of MPH MR treatment.)	45 withdrawals; 2 withdrawals due to adverse events	Celltech Pharmaceuticals, Inc.	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Greenhill 2006	Eligible participants were males and females 6 to 17 years of age who met DSM-IV criteria for ADHD of any type, as established by a psychiatric examination and a semistructured diagnostic interview. For boys, baseline scores on the Conners ADHD/DSM-IV Scale-Teacher version (CADS-T) DSM-IV total subscale were required to be ≥27 for those 6 to 8 years old, ≥24 for those 9 to 11 years old, ≥19 for those 12 to 14 years old, and ≥14 for those 15 to 17 years old. For girls, the respective baseline cutoff scores on the CADS-T were ≥16, ≥13, ≥12, and ≥6. All of the patients were attending school in a classroom setting and had the same teacher for the duration of the study who was able and willing to perform symptom assessments. Patients had to be functioning at age-appropriate levels academically.	d-MPH-ER: Mean Final Dose = 24.0 mg/day (SD 7.1) ; Dose Range: 5-30 mg/day Placebo: Mean Final Dose: 26.9 mg/day (SD 7.1)	NR/NR	Mean age= 10 yrs (Range: 6-17 yrs) 64% male 60.1% white	D-MPH-ER vs. Placebo, NS between groups **DSM-IV ADHD diagnosis N(%)** Inattentive: 22 (21.4) Hyperactive/impulsive: 2 (1.9) Combined Type: 79 (76.7) **Duration of ADHD symptoms, yr** Mean (SD): 5.3 **Received Medication for ADHD in the past N(%)** Yes: 40 (38.8) No: 63 (61.2) **Baseline CADS-T total subscale score** Mean: 34.3 **Baseline CADS-P total subscale score** Mean: 39.5 **Baseline CGI-S rating N(%)** 4: 65 (63.1) 5: 35 (34.0) 6: 3 (2.9)	103	NR/NR/97

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Greenhill 2006	**d-MPH-ER vs. Placebo** Conners ADHD/DSM-IV Scale - Teacher version (CADS-T) total subscale score: 16.3 vs. 5.7, p<0.001 CADS-T Inattentive: 8.1 vs. 3.3, p=0.001 CADS-T Hyperactive-Impulsive: 8.2 vs. 2.5, p<0.001 CADS-P DSM-IV total subscale score: 17.6 vs. 6.5, p<0.001 CADS-P Inattentive: 9.5 vs. 3.2, p<0.001 CADS-P Hyperactive-Impulsive: 8.2 vs. 3.3, p<0.001 CGI-I, very much improved or much improved at final visit: 67.3% vs. 13.3%, p<0.001 CGI-S at final visit: moderately ill: 32.0% vs. 64.0% markedly ill: 4% vs. 21.4% severely ill: 0% vs. 2.4% CHQ physical component: NS CHQ psychological component:11.9 vs. 4.3, p<0.001	D-MPH-ER vs. placebo (%) Total Adverse Events: 75.5 vs. 57.4, NS Decreased appetite: 30.2 vs. 8.5, p=0.0068 Headache: 24.5 vs. 10.6, NS Abdominal Pain, Upper: 13.2 vs. 12.8, NS Nausea: 11.3 vs. 6.4, NS Nasopharyngitis: 9.4 vs. 6.4, NS Upper respiratory tract infection: 9.4 vs. 6.4, NS Dyspepsia: 7.5 vs. 4.3, NS Insomnia: 7.5 vs. 6.4, NS Abdominal Pain: 5.7 vs. 0, NS Initial Insomnia: 5.7 vs. 4.3, NS Affect lability: 3.8 vs. 0, NS Anorexia: 3.8 vs. 2.1, NS Diarrhea: 3.8 vs. 2.1, NS Fatigue: 3.8 vs. 4.3, NS Gastroenteritis: 3.8 vs. 0, NS Influenza: 3.8 vs. 8.5, NS Irritability: 3.8 vs. 2.1, NS Otitis media: 3.8 vs. 2.1, NS Stomach Discomfort: 3.8 vs. 0, NS Vomiting: 3.8 vs. 4.3, NS	19/1	Novartis Pharmaceuticals Corporation	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Greenhill 2006	6 to 17 years of age, inclusive; DISC-IV was used to establish the patients' diagnosis of ADHD using the full DSM-IV diagnostic criteria; CGI-S rating of 4 or higher (moderately ill or worse); weight and height between the 5th and 95th percentile based on the National Center for Health Statistics; intelligence quotient of at least 80; absence of learning disabilities, with a score of at least 80 on the Wechsler Individual Achievement Test; attending a full-time school (not home school), with a teacher and parent or legal guardian willing to participate; and total and/or factor scores on the teacher-/investigator-rated ADHD-RS-IV School Version at least 1.5 standard deviations above the norm for the patient's age and gender.	Modafinil: Mean Dose: 361.4 mg (SD 90.9) Dose Range: 85 to 425mg Placebo: Mean Dose: 383.1 mg (SD 85.5) Dose Range: 85 to 425mg	none/NR	Mean age= 9.9 yrs (Range: 6 - 16 yrs) 73% male 72% white	Modafinil vs. Placebo **CGI-S Score, N(%)** Moderately ill: 76 (38) Markedly ill: 87 (44) Severely ill: 34 (17) Not Assessed: 1 (0.5) **Current ADHD Subtype, N(%)** Inattentive: 47 (24) Hyperactive/impulsive: 10 (5) Combined: 139 (70) **Previous ADHD Treatment, N(%):** 109 (55) MPH: 73 (37) Amph. Salts: 64 (32) ATX: 27 (14) Other: 22 (11) **Most Frequently Coadministered Agents N(%)** Nonopioid analgesics/anti-inflammatories: 65 (33) Respiratory agents: 33 (17) Antihistamines: 28 (14) Anti-infectives: 24 (12) **ADHD-RS-IV total score, mean** School Version: 38.5 Home Version: 40.8	200	59/5/194

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Greenhill 2006	Modafinil vs. placebo , mean change **ADHD-RS-IV School version** Total score: -17.5 vs.-9.8, p<.0001 Inattention: -9.7 vs. -4.9, p<.0001 Hyperactivity/impulsivity: -7.9 vs. -4.8, p=.003 **ADHD-RS-IV Home version** Total score: -17.6 vs. -7.7, p<.0001 Inattention: -9.2 vs. -3.5, p<.0001 Hyperactivity/impulsivity: -8.3 vs. -4.2, p=.0001 TOVA **ADHD score**: -0.4 vs. 1.1, p=.001 **CPRS:R-S** **ADHD index**: -12.7 vs. -6.3, p=.001	Modafinil vs. Placebo, N(%) Insomnia : 37(28) vs. 5(7), p<.05 Headache : 29(22) vs. 6(9), p<.05 Decreased appetite: 23(18) vs. 2(3), p<.05 Abdominal pain: 16(12) vs. 3(4), NS Infection: 14(11) vs. 6(9), NS Increased cough: 12(9) vs. 6(9), NS Pharyngitis: 11(8) vs. 9(13), NS Rhinitis: 10(8) vs. 7(10), NS Vomiting: 8(6) vs. 4(6), NS Emotional Lability: 7(5) vs. 4(6), NS Nervousness: 7(5) vs. 3(4), NS Weight Loss: 7(5) vs. 0(1), p<.05 Accidental Injury:6(5) vs. 3(4), NS Fever: 6(5) vs. 3(4), NS Gastroenteritis: 6(5) vs. 3(4), NS Somnolence: 6(5) vs. 3(4), NS Nausea: 6(5) vs. 2(3), NS	59/10	NR	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	Stimulant naive, children of both sexes, ages 3 to 5.5 years with a DSM-IV consensus diagnosis of ADHD based on the Diagnostic Interview Schedule for Children IV-Parent Version and semistructured interview; combined or predominantly hyperactive subtype; an impairment scale score G55 on the Children`s Global Assessment Scale; hyperactive-impulsive subscale T score of 65 (1.5 SDs above the age- and sex-adjusted means) on both the Revised Conners Parent and Teacher Rating Scales; Full Scale IQ equivalent of 970 on the Differential Ability Scales; participation in a preschool, day care group setting, or other school program at least 2 half-days per week with at least eight same-age peers; and the same primary caretaker for at least 6 months before screening. To be eligible, patients met both dimensional symptom criteria (scores 91.5 SD above age- and gender-adjusted means on the Hyperactive/Impulsive subscale of both parent and teacher Conners Rating Scales) and categorical diagnostic criteria (positive diagnosis on Diagnostic Interview Schedule for Children-IV and semistructured diagnostic interview).	Various- Methylphenidate (3.75 to 22.5 mg daily) vs. placebo , 70-week trial	none	Baseline n= 303 Mean age=4.41 yrs Gender: 76% male Ethnicity: 63% white 19% black 16% Hispanic or Latino 2% Asian 0.7% other Phase 5-Crossover n = 165 Mean age=4.74 yrs Gender: 69% male Ethnicity: 63% white 18% black 18% Hispanic or Latino 1% Asian 0.6% other Phase 6 Parallel n =114 Mean age=4.76 yrs Gender: 70% male Ethnicity: 65% white 17% black 17% Hispanic or Latino 0.9% Asian 0.9% other	Conners Teacher rating scale (mean) Baseline 38.52 Phase 5 40.16 Phase 6 39.95 Conners Parent rating scale (mean) Baseline 35.43 Phase 5 35.91 Phase 6 35.48	165	1-week open-label lead-in (*n* = 183); a 5-week placebo-controlled, double-blind phase (*n* = 165); a 5-week double-blind, parallel phase (*n* = 114); and 10 months of open-label maintenance (*n* = 140 entered, 95 completed)

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	Phase 5 - decreases in ADHD symptoms were found on MPH vs. placebo at 7.5 mg (p < .01), 15 mg (p < .001), and 22.5 mg (p < .001) doses, but not for 3.755 mg (p < .06). The mean optimal MPH total daily dose for the entire group was 14.2 mg/day Parallel study phase 6, only 21% on best-dose MPH and 13% on placebo achieved MTA-defined categorical criterion for remission	Overall AEs per parents: 30% of parents reported moderate to severe AEs during study. MPH 15mg vs. placebo Appetite decrease chi-squared 5.4 P < 0.03 Trouble sleeping chi-squared 5.4 P < 0.03 MPH 22.5mg vs. placebo Weight loss chi-squared 4.0 P < 0.05 Severe AEs at baseline (2), open lead-in (23), titration (38), parallel (2), and maintenance (14) and overall there were 8 serious AEs throughout	Total withdrawals Parallel phase- placebo 45% MPH 15% Due to AEs Overall 11% (21) Open lead-in 11 Titration 3 Parallel Phase 1/114 Open label maintenance 7/140	National Institutes of Mental Health; Author's relationships with Pharma are disclosed (long list)	Withdrawals were not reported well

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Grizenko 2006	Diagnoses of ADHD according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), 31 that were based on clinical examination, information collected from different sources and a structured interview using the Diagnostic Interview Schedule for Children Version IV (DISC-IV). Children with an IQ lower than 70 on the Wechsler Intelligence scale for Children-III,32 a history of Tourette's syndrome, pervasive developmental disorder or psychosis were excluded from the study.	Placebo or 0.5 mg/kg of body weight of MPH divided in 2 equal doses (morning and noon)	NR	Mean Age: 9.2 yrs (Range: 6 -12 yrs) Male: 85.3% Ethnicity: NR	IQ Mean: 96.45 CBCL ext. mean: 70.0 CBCL int. mean: 63.5 RASS Mean: 43.8 CPT overall index: 10.6 44% with learning disability and 56% without learning disability LD determined using the Wide range Achievement Test (WRAT) and if there was a difference in reading or math grade level >/= 2 years with respect to the expected grade level, the child was considered to have an LD in that subject.	95	NR/NR/95
Gross-Tsur 1997 Israel (Poor)	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).	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	Mean age=9.8 18 (60%) male Ethnicity NR	Mean IQ=92.8 Complex partial seizures=15 (50%) Primary tonic-clonic seizures=7 (23.3%) True absences=6 (20%) Multiple seizure type=2 (6.7%) Monotherapy=26 (86.7%) Combination therapy=4 (13.3%) Abnormal brain computed tomography=4 (13.3%)	30	NR/NR/30 for all but AED drug levels (n=27)

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Grizenko 2006	Responders=CCR of 2 or 3 and Non-responders=CCR of 0 or 1, number(%) Non-responders with LD: 19 (45) [with RD and MD: 10 (45), with RD only: 4 (33), with MD only: 5 (63)], without LD: 13 (25), p=0.034 Responders with LD: 23 (55) [with RD and MD: 12 (55), with RD only: 8 (67), with MD only: 3 (37)], without LD: 40 (75) Reading: with RD non-responders: 14(41), responders: 20(59) and without RD nonresponders: 19(31), responders 41(68), p=0.33 Math: with MD non-responders: 15(50), responders: 15(50) and without MD nonresponders: 18(28), responders 47(72), p=0.034	No important AE or side effects were noted	NR; none	Canadian Institutes of Health Research	
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)	AE's reported only for the observational study periods.	NR NR	NR	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Hall 1973	Male outpatients; with pre-drug age 72-132 months; normal IQ (WISC 80 or above); personality and adjustment difficulties as indicated by one or more combinations of the following behaviors: excitable, impulsive, poor judgment, learning achievement not commensurate with measures of general intelligence, restless or immature, low frustration tolerance, distractibility, short attention span emotional lability, mood changes quickly, clumsy, poor motor coordination; free of observable psychotic behaviors; general diagnostic category due to minimal brain dysfunction.	Desoxyephedrine (time released formula) 5 mg/day taken in morning for first 2 weeks Dose increase to 10 mg/day for following 2 weeks (one child required 15mg dose)	NR	Mean age: 6.9 yrs. 100% male 93% white	**Class placement, N (%)** regular: 21 (65.6) educationally handicapped: 4 (12.5) limited day: 3 (9.4) aphasia: 2 (6.3) home teacher: 2 (6.3) previously medicated, N (%) Yes: 8 (25) No: 24 (75)	32	NR/NR/32
Handen 1991	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	week3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid (breakfast and lunch) for a 7-days period.	NR	Mean age=8.6, range 6.7-12.1 years Gender=22(81.5%) male Race: NR	100% mental retardation and ADHD	27	13 withdrawn/ o lost to fu/ 27 analyzed

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Hall 1973	**desoxyephedrine vs. placebo, mean change** **PALT** Trials: 0.37 vs 1.82 Errors: -1.94 vs. 11.13 **MFFT** Latency: 2.47 vs. -1.50 Errors: -6.75 vs. -0.87 **PM** TA: 1.25 vs. 0.60 TQ: 8.19 vs. 4.75 **Digit Span:** 0.44 vs. 0.76 **WISC** Verbal IQ: 7.17 vs. -0.75 Perf. IQ: 10.31 vs 5.25 FS IQ: 8.19 vs. 2.43 **WW:** -8.62 vs. -1.25	NR	NR/NR	Abbott Labs (partial funding)	dissertation
Handen 1991	18(67%) were identified as responders to methylphenidate. Placebo vs. 0.3mg/kg (N=27); Placebo vs. 0.6mg/kg (N=25) Irritability: NS; 14(51.8%): 3(12%), p<0.05 Anxiety: NS; 11(40.7%): 3(12%), p<0.05 High activity: 21(77.8%): 9(33.3%), p<0.05; 21(77.8%): 10(40%), p<0.05 *Other side effects: NS; NS Placebo vs. 0.3mg/kg (N=14); Placebo vs. 0.6mg/kg (N=14) Staring: 2.0: 0.93, p<0.05; 2.0: 0.75, p<0.05 Irritability: 1.21:0.43, p<0.05; 1.21: 0.33, p<0.05 Anxiety: 1.0: 0.86, NS; 1.0: 0.50, p<0.05 Moody: 0.79: 0.36, NS; 0.79: 0.00, p<0.05 High activity: 3.0: 1.50, p<0.05; 3.0: 0.75, p<0.05 *Other side effects: NS; NS	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	Edith L. Trees Foundation and Research Advisory Committee of Children's Hospital of Pittsburgh	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Handen 1997	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.	methylphenidate (MPH) *no dosage, duration and schedule information	NR	Age (months): mean=130.4, range 86-178 Gender: 32(62.7%) male Race: 37(72.5%) Caucasian, 13(25.5%) Black, 1(2%) Hispanic	Mean IQ =64(8.6), range 48-77 Hollingshead four-factor Index for social-economic status (Level): I -- 3(5.9%) II -- 10(19.6%) III -- 14(27.5%) IV -- 6(11.8%) V -- 18(35.3%)	51	0/0/0
Handen 1999	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.	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.	NR	Age: mean=4.9, range 4-5.11 years Gender: 9(82%) male Race: NR	Mean IQ=60(11.6), range 40-78 Comorbidities: ADHD: 9 (82%) Oppositional defiant disorder: 2 (18%)	11	1 withdraw/ 0 lost/ 10 analyzed

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Handen 1997	Initial vs. follow-up: Conduct problem (CA), p=0.041 Conduct problem (MA), p=0.097 Anxiety (CA), p=0.295 Anxiety (MA), p=0.041 Impulsivity-Hyperactivity (CA), p=0.003 Impulsivity-Hyperactivity (MA), p=0.007 Learning problem (CA), p<0.005 Learning problem (MA), p<0.005 Psychosomatic (CA), p=0.947 Psychosomatic (MA), p=0.569 Hyper. Index (CA), p<0.005 Hyper. Index (MA), p<0.005	NR	NR	National Institute of Child Health and Human Development; US DHHS	
Handen 1999	8(73%) responded to the drugs (based on a 40% or more decrease in Teacher-rated Conners Hyperactivity Index and/or Hyperactive-Distractible subscale) Dull, social withdrawal, poor appetite, anxiety, and drowsiness were reported more in the drugs than placebo (mean): Dull -- placebo(0.4), 0.3mg/kg(1.5), 0.6mg/kg(2.2) Social withdrawal -- placebo(0.4), 0.3mg/kg(1.3), 0.6mg/kg(2.1) Poor appetite -- placebo(0.1), 0.3mg/kg(1.9), 0.6mg/kg(3.2) Anxiety --placebo(0), 0.3mg/kg(0.1), 0.6mg/kg(0.3) Drowsiness -- placebo(0), 0.3mg/kg(1.1), 0.6mg/kg(0.6)	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%)	Fanny Pushin Rosenberg Research Foundation	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Hazell 2006	Children and adolescents aged 6–15 years who met DSM-IV criteria for ADHD, as assessed by clinical interview and confirmed by a structured diagnostic interview. In addition, all patients had symptom severity at least 1.5 standard deviations above expected age and sex norms on the ADHD Rating Scale-IV (ADHD RS) for the patients' ADHD subtype (predominantly inattentive, predominantly hyperactive/impulsive, combined). Children and adolescents were randomly assigned in the double-blind, placebo-controlled relapse prevention study period if they were deemed responders to 10 weeks of open-label treatment with atomoxetine.	ATX: Minimum dose of 0.5mg/kg/day to a maximum of 1.8 mg/kg/day Mean Dose = NR	NR/NR	Mean Age: NR (Range: 6–15 yrs) Male: 90% Ethnicity: 98% Caucasian	ODD vs. non-ODD **ADHD Subtype, No.(% of total in ODD or non-ODD group)** Hyperactive/impulsive: 19(4.6) Inattentive: 93 (22.4) combined: 303 (73) **previous stimulant therapy, No.(% of total in ODD or non-ODD group)**: 218 (52.5) ADHD only: 236 ADHD + ODD: 179	416	211/5/415
Hunt 1985/Hunt 1986	A child had to meet DSM-III criteria for ADD-H and score at least 2.0 standard deviation (SD.) 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.	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/ no other types of interventions used.	10 children age mean 11.6 years. Gender, ethnicity, etc NR.	100% receiving special education services, 70% had been previously treated with stimulant medication for ADHD	10	0/0/10

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Hazell 2006	**ADHD with ODD vs. ADHD without ODD taking Atomoxetine: RR 0.67, 95% CI 0.42-1.06** Mean days to relapse: 215 vs. 211, p=0.08 **ADHD with ODD vs. ADHD without ODD taking Placebo: RR 1.27, 95% CI 0.81-1.99** Mean days to relapse: 136 vs. 151, p=0.22	NR	211/10	Lilly	original "parent study" reports detailed outcomes and safety data, Michelson et al 2004
Hunt 1985/Hunt 1986	Clinicians results not rated statistically. Connors's Ratings of Teachers 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. Changes of conduct before vs after treatment: p=.4. Changes in inattention before vs after treatment: p=.5. Connor's Ratings of Parents 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)	90% (9 children) reported sleepiness in first hour after dose. Mean blood pressure decreased 10% on clonidine. 10% (1 child) reported increased depressive symptoms on clonidine. 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)	None	NR	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Jain 2011 U.S.	Patients 6 to 17 years of age with a diagnosis of ADHD of the hyperactive or combined inattentive/hyperactive subtype according to criteria set forth in the DSM-IV and each patient's clinical research physician, and a minimum score of 26 on the ADHD-RS-IV.	A: CLON-XR 0.2 mg/day B: CLON-XR 0.4 mg/day C: Placebo for 8 weeks Dosing schedule: A forced dose-escalating titration schedule of 0.1 mg/day per week was used to achieve the target dose for the patient, followed by dose tapering in 0.1-mg/day/week intervals until cessation of treatment at the end of week 8. Patients who experienced AEs warranting dose reduction were discontinued from the study.	Did not report exactly what was allowed, but states that the most commonly used class of concomitant medications was cough and cold preparations (11.4%), which were more commonly used in the CLON-XR 0.2-mg/day group (16%) than in the placebo (10%) and CLON-XR 0.4-mg/day (8%) groups. Patients in the CLON-XR 0.2-mg/day group also had greater use of systemic antibacterial agents, antiinflammatory products, and antirheumatic products than the placebo or CLON-XR 0.4-mg/day groups.	Mean age: 9.5 years (range 6-17) Male: 72.4% White: 59.2% Black/African-American: 27.2% Hispanic/Latino: 8.3% Other: 5.3%	Mean weight: 41.1 kg Mean ADHD-RS-IV total score: 44.5	236	91/12/228

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Jain 2011 U.S.	Placebo vs CLON-XR 0.2 mg/day vs CLON-XR 0.4 mg/day **Mean Change in ADHD-RS-IV from Baseline to Week 5 (ITT Population):** *LOCF method:* Total score, mean (SD): -7.5 (9.41) vs -15.6 (12.96; P<0.0001) vs -16.5 (13.54; P<0.0001) Hyperactivity Subscale score, mean: -4.1 vs -7.9 (P=0.0012) vs -8.8 (P=0.0002) Inattention Subscale score, mean: -3.4 vs -7.7 (P=0.0011) vs -7.7 (P=0.0006) *Observed Case method:* Total score, mean (SD): -8.0 (9.16) vs -16.5 (12.08; P<0.0001) vs -19.4 (12.75; P<0.0001) Hyperactivity Subscale score, mean: -4.5 vs -8.3 (P=0.0017) vs -10.1 (P<0.0001) Inattention Subscale score, mean: -3.5 vs -8.2 (P=0.0003) vs -9.3 (P<0.0001) *Mixed Model for Repeated Measures method:* Total score, mean: -8.0 vs -16.5 (P<0.0001) vs -19.4 (P<0.0001) ADHD-RS-IV treatment effect size by dose: NA vs 0.713 (95% CI, 0.38 to 1.04) vs 0.766 (95% CI, 0.44 to 1.09) Discontinuations because of lack of efficacy: 32% vs 9% vs 11% Change from baseline to week 5, CLON-XR was significantly greater than placebo for CPRS-R total score, CGI-S, CGI-I, and PGA assessment. Mean improvement in CPRS-R total score was significantly greater than placebo in both CLON-XR groups (P≤0.0122) at weeks 3 and 5. In addition, improvement in CGI-S and CGI-I from baseline to week 5 was significantly greater in both treatment groups versus placebo (P≤0.0001 for CGI-S and P≤0.0032 for CGI-I). Significant improvement in PGA score from baseline in both treatment groups versus placebo was also observed as soon as week 2 (P≤0.0001) and was maintained through week 7 (P≤0.0227) in the CLON-XR 0.2-mg/day group and through week 5 in the CLON-XR 0.4-mg/day group (P≤0.0099).	Placebo vs CLON-XR 0.2 mg/day vs CLON-XR 0.4 mg/day Treatment-Emergent AEs that occurred in ≥5% of treatment groups: Somnolence: 5 (6.6%) vs 30 (39.5%) vs 24 (30.8%) Fatigue: 1 (1.3%) vs 12 (15.8%) vs 10 (12.8%) Irritability: 3 (3.9%) vs 7 (9.2%) vs 6 (7.7%) Pharyngolaryngeal pain: 3 (3.9%) vs 6 (7.9%) vs 6 (7.7%) Increase in body temperature: 2 (2.6%) vs 4 (5.3%) vs 2 (2.6%) Insomnia: 1 (1.3%) vs 4 (5.3%) vs 5 (6.4%) Ear pain: 1 (1.3%) vs 4 (5.3%) vs 0 (0%) Emotional disorder: 1 (1.3%) vs 3 (3.9%) vs 4 (5.1%) Nightmare: 0 (0%) vs 3 (3.9%) vs 7 (9.0%) Constipation: 0 (0%) vs 1 (1.3%) vs 5 (6.4%) Dry mouth: 1 (1.3%) vs 0 (0%) vs 4 (5.1%)	Placebo vs CLON-XR 0.2 mg/day vs CLON-XR 0.4 mg/day Total withdrawals: 37 (47.4%) vs 24 (30.8%) vs 32 (40%) Due to AE: 1 (1.3%) vs 5 (6.4%) vs 15 (18.8%)	Addrenex Pharmaceuticals, Inc. (a Shionogi company)	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Kahbazi 2009 Iran	Boys and girls between 6 and 15 years who clearly met DSM-IV -TR diagnostic criteria for ADHD, total and/or subscale scores on the ADHD-RS-IV at least 1.5 standard deviations above norms for patient's age and gender. All patients had combined subtype and newly diagnosed.	A. Modafinil 200-300mg/d B. Placebo Time period: 6 weeks	NR	Age: 9.1 years Male: 76.1% Persian: 100%	Weight::28.8 kg	46	3/2/NR
Kaplan 2004 U.S. ODD/ADHD subset analysis of Spencer 2002	Patients were 7-13 years and met diagnostic criteria for ADHD as defined by DSM-IV and met diagnostic criteria for ODD as characterized by DICA-IV and confirmed by clinical assessment according to the DSM-IV criteria. All children had an IQ in the normal range, as measured by the WISC-III.	See Spencer 2002 Atomoxetine (n=53) Placebo (n=45) Max dose was the lower of either 2 mg/kg/d or 90 mg/d Mean total daily dose: 55.3 mg (SD = 19.0) Treatment as follows: 2 week medication washout (visits 1-3), then a 9-week DB treatment phase (visits 3-12) and then a 1 week single blind discontinuation phase (visits 12-13).	NR	Mean age: 9.98 years 79.6% male Ethnicity: NR	Mean WISC-III Full scale IQ: 104.9 Mean ADHD-RS Total score: 42.1 ADHD-RS Inattentive subscale: 22.0 ADHD Hyperactive/Impulsive subscale:20.0 CGI-ADHD-S: 5.15 Conners Parents RS: ADHD Index: atomoxetine 27.3 vs placebo 28.6 All patients (n=98) in this subset had ODD	see Spencer 2002	in this subset, 24 / NR / 98

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kahbazi 2009 Iran	Modafinil vs placebo Parent ADHD rating scale Mean (SD) change from baseline in Parent ADHD rating scale score: -22.47 (8.92) vs -8.21 (6.15), t=6.30, df=44, p<0.001. difference between 2 groups indicated by the effect of group, between subjects factor F=38.07, df=1, p<0.001, effect size=0.92 Difference between modafinil vs placebo in change from baseline t=6.30, df=44, p<0.001 Proportion of responders with at least 40% decrease in Parent ADHD rating scale score: 78.26% vs 0% Teacher ADHD rating scale Mean (SD) change from baseline in Teacher ADHD rating scale: -23.26 (8.15) vs -7.69 (5.04), t=7.78, df=44, p<0.001, difference between 2 groups t=8.00, df=44, p<0.001, difference between 2 groups indicated by the effect of group, between subjects factor F=38.15, df=1, p<0.001, effect size=0.92. Difference between modafinil vs placebo in change from baseline t=7.78, df=44, p<0.001 Proportion of patients with at least 40% decrease in Teacher ADHD rating scale 78.26% vs 0%	Modafinil vs placebo Abdominal pain: 8.7% vs 4.3% Anxiety, nervousness: 8.7% vs 8.7% Decreased appetite: 30.4% vs 8.7%, p=0.05 Difficulty falling asleep: 17.4% vs 8.7% Weight loss: 8.7% vs 4.3% Nausea: 8.7% vs 8.7% Dry mouth: 17.4% vs 13% Irritability: 8.7% vs 4.3% Headaches: 8.7% vs 4.3%	Modafinil vs placebo Total withdrawals:4.3% vs 13% Withdrawals due to AE: NR vs 0% (1 withdrawal from modafinil group, reason not stated)	Grant 3317 Tehran University of Medical Sciences	
Kaplan 2004 U.S. ODD/ADHD subset analysis of Spencer 2002	Mean change in scores, baseline to endpoint, atomoxetine vs placebo: ADHD RS Total : -17.0 vs -7.5, p<0.001 (effect size=0.72) Inattentive subscale: -8.7 vs -3.9, p<0.001 (effect size=0.71) Hyperactive/Impulsive subscale: -8.3 vs -3.6, p=0.002 (effect size=0.66) CGI-ADHD-Severity: -1.5 vs -0.7, p=0.003 Conners' Parent rating scale and subscale scores: ADHD Index: -7.7 vs -3.2, p=0.005 Cognitive: -4.1 vs -1.6, p=0.006 Hyperactive: -4.3 vs-1.3, p=0.003 Oppositional: -2.4 vs -1.8 p=0.796	AEs with significant differences, atomoxetine vs placebo: Decreased Appetite: 18.9% vs 2.2%, p<0.01 Emotional Lability: 11.3% vs 0.0%, p=0.03 Other AEs: atomoxetine vs placebo: Abdominal pain: 28.3% vs 22.2%, p=0.643 Headache: 28.3% vs 28.9%, p>0.99 Rhinitis: 24.5% vs 35.6%, p=0.271 Pharyngitis: 18.9% vs 15.6%, p=0.791 Nausea: 15.1% vs 11.1%, p=0.766 Nervousness: 15.1% vs 6.7%, p=0.271 Vomiting: 15.1% vs 15.6%, p>0.99 Cough increased: 11.3% vs 8.9%, p=0.75 Diarrhea: 11.3% vs 8.9%, p=0.75 Somnolence: 11.3% vs 6.7%, p=0.501 Fever: 7.5% vs 13.3%, p=0.505	24 (12 per group) ; 5 (3 in atomoxetine and 2 in placebo)	NR	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Kelsey 2004	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.	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.	NR/NR	Children aged 6-12 years/71% enrolled were male/ ethnicity NR.	ADHD Subtypes Combined: 37.6% of atomoxetine, 67.2 % of placebo Hyperactive/impulsive: 3.8% atomoxetine, 3.1% of placebo Inattentive: 26.3% of atomoxetine, 29.7% of placebo Oppositional/defiant disorder: 37.6% of atomoxetine group; 29.7% of placebo group Conduct disorder: 5.3% of atomoxetine group; 1% of placebo group	197	Atomoxetine: 26 withdrawn 4 lost to fu 107 analyzed Placebo: 17 withdrawn 3 lost to fu 47 analyzed

Evidence Table 3. Data abstraction of placebo-controlled trials in children

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

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Klein 1988 (Poor)	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	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	Mean age=9 years 91% male Ethnicity NR	Height=133.4 cm Weight=27.9 kg	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)
Klorman 1987/Coons 1986 (Fair)	Scored 1.5 on the abbreviated Conners Hyperactivity Questionnaire and 1.02 on the Home Activity Scale	Methylphenidate or placebo 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	NR	Mean age=14.80 years Gender: 84.2% male Ethnicity: NR	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)	19	0/0/19

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Klein 1988 (Poor)	NR	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	Supported in part by Public Health Service grant MH 18579	Retrospective analysis of height/weight data from a study designed to measure efficacy
Klorman 1987/Coons 1986 (Fair)	<u>Parent rating (mean dose)</u>, placebo: methylphenidate Conners Scale= 1.35: 0.89, p<0.03 I/O=1.30: 0.89, p<0.05 A=1.36: 1.02, p<0.09 <u>Teacher rating (mean dose)</u>, placebo: methylphenidate, all NS; <u>Teacher rating (Week 3 dose)</u>, 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 <u>Heart rate:</u> rose under drug condition (100 beats/min), p<0.02 <u>Sternberg Test</u>: methylphenidate decreased errors and reaction time on performance, p<0.0001 <u>CPT</u>: methylphenidate reduced the rate of missed targets on performance, p<0.0001; enhanced the index of sensitivity of detection, p<0.0005; shorten P3b latency, p<0.0001	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, pronunciation, clumsiness, restlessness, fatigue, sleepiness, sleep problem, crying, irritability, unhappiness, sadness, inattention.	0	NIMH Grants MH 32103 and MH38118	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Klorman 1990/Klorman 1991/Klorman 1992 (Fair)	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 and 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 Scale WISC-R IQ scores > 80 on a test administered within 6 months of referral. Subjects were in good physical health and free of all medication.	Methylphenidate and placebo 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(baseline, placebo, drug) Mean dosage: 35.33mg/day, or 0.64mg/kg/day	NR	Mean age=14.12 years Gender: 87% male Ethnicity: 96% Caucasian	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)	48	NR/NR/48

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
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 significantly 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	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	NIMH grant MH38118	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Kollins 2011 U.S.	Children and adolescents with hyperactive- or combined-subtype ADHD who had an inadequate response to their stable stimulant regimen (i.e., methylphenidate or amphetamine) defined as a total score ≥26 on the ADHD-RS-IV questionnaire after ≥4 weeks.	A: Clonidine XR 0.1-0.4 mg/day + baseline stimulant medication B: Placebo + baseline stimulant medication for 8 weeks	Concomitant use of antihypertensive medications, psychotropic drugs, oral corticosteroids, sedating antihistamines, antidiabetic medications, diet aids, and bronchodilators ≤3 days per week.	Mean age: 10.4 years (SD 2.5) Male: 73.6% White: 53.8% Black: 27.4% Hispanic: 11.2% Other: 7.6%	Weight: 39.6 kg (SD 16.2) ADHD-RS-IV total score: 38.9 (SD 7.3) Using methylphenidates: 59.9% Using amphetamines: 40.6%	198	33/1/197

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kollins 2011 U.S.	Placebo + Stimulant vs Clonidine-XR + Stimulant Change (improvement) from baseline to week 5: ADHD-RS-IV, mean (SD): Total change: -11.5 (12.2) vs -15.7 (12.3); P=0.009 Inattention subscale: -5.8 (6.8) vs -7.8 (6.8); P=0.017 Hyperactivity/impulsivity subscale: -5.8 (6.3) vs -7.9 (6.7); P=0.014 CPRS, mean (SD): Total change: -27.1 (38.2) vs -40.2 (41.4); P=0.017 Hyperactivity subscale: -3.8 (5.7) vs -5.8 (6.5); P=0.017 Oppositional subscale: -3.6 (6.3) vs -5.1 (6.6); P=0.062 CGI-S, mean (SD): -1.2 (1.3) vs -1.5 (1.2); P=0.021 CGI-I, mean (SD): 3.0 (1.2) vs 2.5 (1.2); P=0.006 PGA, mean (SD): 3.4 (1.4) vs 2.7 (1.3); P=0.001 Percentage of patients considered responders at week 7: 25% vs 42%; P=0.0126 Change in stimulant dosage: No change: 73% vs 67% Increased: 18% vs 19% Decreased: 10% vs 15% Placebo + methylphenidate vs Clonidine-XR + methylphenidate vs Placebo + amphetamine vs Clonidine-XR + amphetamine Improvement from baseline in ADHD-RS-IV total score: -10.4 vs -14 vs -13.5 vs -18.2; P=NS	Placebo + methylphenidate vs Clonidine-XR + methylphenidate vs Placebo + amphetamine vs Clonidine-XR + amphetamine Treatment-emergent AEs with 5% or greater incidence in the CLON-XR + stimulant group: Somnolence: 6 (10%) vs 13 (22%) vs 2 (5%) vs 7 (16%) Headache: 12 (20%) vs 10 (17%) vs 8 (22%) vs 9 (21%) Fatigue: 2 (3%) vs 7 (12%) vs 2 (5%) vs 9 (21%) Upper abdominal pain: 6 (10%) vs 4 (7%) vs 2 (5%) vs 8 (19%) Nasal congestion: 6 (10%) vs 4 (7%) vs 0 (0%) vs 5 (12%) Pharyngolaryngeal pain: 4 (7%) vs 4 (7%) vs 0 (0%) vs 4 (9%) Cough: 6 (10%) vs 2 (3%) vs 2 (5%) vs 4 (9%) Irritability: 6 (10%) vs 1 (2%) vs 3 (8%) vs 4 (9%) Insomnia: 2 (3%) vs 2 (3%) vs 1 (3%) vs 2 (5%) Increased body temperature: 1 (2%) vs 1 (2%) vs 1 (3%) vs 4 (9%) Dizziness: 0 (0%) vs 3 (5%) vs 2 (5%) vs 2 (5%)	Placebo + Stimulant vs Clonidine-XR + Stimulant Total withdrawals: 22 (22.9%) vs 11 (10.8%) Due to AE: 3 (3.1%) vs 1 (0.98%)	Addrenex Pharmaceuticals Inc.	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Kratochvil 2011 U.S.	5- and 6-year-old children with ADHD and symptoms present for ≥9 months; a T score of ≥65 on the ADHD-RS; a CGAS score of ≥55; and attending day care, preschool, kindergarten, or elementary school for ≥2 half-days per week with a peer group of 8 or more.	A: Atomoxetine 0.5-1.8 mg/kg/day, mean 1.4 mg/kg (SD 0.4) B: Placebo for 8 weeks	NR (excluded patients with concurrent use of psychotropic or other medications with significant central nervous system effects, but also says that concomitant medications were assessed at each visit)	Mean age: 6.1 years Male: 67.7% Hispanic or Latino: 19.4% Not Hispanic or Latino: 80.6% White: 86% Black or African American: 10.8% American Indian: 3.2%	ADHD subtype: Inattentive: 8.6% Hyperactive/impulsive: 9.7% Combined: 81.7% Comorbidities: Oppositional defiant disorder: 34.4% Enuresis: 17.2% Separation anxiety: 1.1% Phobia: 8.6% Tics: 1.1% Other: 5.4%	101	26/3/93

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kratochvil 2011 U.S.	Placebo vs Atomoxetine ADHD-RS 8 week change from baseline, mean (SEM): Parent total: -5.8 (1.2) vs -13.2 (1.7); P=0.009 Parent hyperactivity: -2.8 (0.8) vs -6.2 (1.0); P=0.005 Parent inattentive: -2.5 (0.8) vs -7.3 (0.8); P=0.002 Teacher total: -5.0 (1.4) vs -12.5 (1.7); P=0.02 Teacher hyperactivity: -3.2 (0.9) vs -5.4 (1.0); P=0.08 Teacher inattentive: -2.3 (0.8) vs -6.6 (1.0); P=0.04 Subjects with CGI-I scores of very much improved or much improved relative to baseline at week 8: 22% vs 40%; P=0.1. Subjects with CGI-S scores of moderately, markedly, or severely ill at study completion: 77% vs 62%; P=0.1 Change in weight: 0.6 kg (SD 0.2) vs -0.2 kg (SD 0.1); P=0 .0006	Placebo vs Atomoxetine Aches/pains: 7 (14%) vs 6 (14%); P=0.9 Affective flattening/blunting: 2 (5%) vs 2 (4%); P=0.9 Allergy: 1 (2%) vs 1 (2%); P=0.9 Anxiety: 1 (2%) vs 1 (2%); P=0.9 Attention/hyperactivity: 6 (12%) vs 3 (7%); P=0.5 Auditory: 2 (4%) vs 2 (5%); P=0.9 Constipation: 1 (2%) vs 0 (0%); P=0.9 Decreased appetite: 4 (8%) vs 13 (30%); P=0.008 Dermatological: 5 (10%) vs 6 (14%); P=0.6 Disruptive behaviors: 4 (9%) vs 3 (7%); P=0.9 Gastrointestinal upset: 8 (16%) vs 17 (39%); P=0.02 Insomnia: 3 (6%) vs 1 (2%); P=0.6 Mood lability :11 (22%) vs 18 (41%); P=0.06 Respiratory: 4 (8%) vs 5 (11%); P=0.7 Sedation: 5 (10%) vs 13 (30%); P=0.02 Self-harm: 1 (2%) vs 1 (2%); P=0.9 Weight loss: 2 (4%) vs 2 (5%); P=0.9 Other: 10 (20%) vs 6 (14%); P=0.4	Placebo vs Atomoxetine (ITT) Total withdrawals: 10 (20.4%) vs 8 (18.2%) Due to AE: 3 (6.1%) vs 0 (0%)	University of Nebraska Medical Center by National Institute of Mental Health grant 5K23MH06612701, and contracts between Eli Lilly and Duke University Medical Center and Columbia University/New York State Psychiatric Institute.	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
McGough 2006	Eligible participants were children between the ages of 6 and 12 years, inclusive, diagnosed with ADHD by Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria. Diagnosis of ADHD and screening for co-occurring psychopathology was based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Present and Lifetime Version (KSADS-PL) and comprehensive clinical psychiatric interviews. The Kaufman Brief Intelligence Test (KBIT) was used to assess mental capacity.	Methylphenidate: Total daily doses of 10, 16, 20, or 27 mg, delivered over the 9-hour patch wear time Mean Dose: NR	NR/NR	Mean age= 9.1 yrs (SD .7) 72% male 70% white	**ADHD subtypes n (%)** Inattentive: 13 (17) Hyperactive/Impulsive: 4 (5) combined: 62 (79) **ADHD Rating Scale, Mean (SD):** 41.8 (7.6) **CGI-S, Mean (SD)**: 4.4 (0.7) Patients with concurrent ODD allowed, proportion of ODD patients not reported	93	13/2/79

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
McGough 2006	**Teacher Rating Treatment/Period/Sequence/Subject-within-sequence,** SKAMP-D, F(1.77): 71.48(p<.0001)/1.25(p=.2664)/.79(p=.3767)/3.26(p<.0001) SKAMP-A, F(1.77): 83.04(p<.0001)/.97(p=.3266)/1.56(p=.2156)/4.98(p<.0001) PERMP-number attempted, F(1.77): 46.34(p<.0001)/3.81(p=0544)/1.42(p=2365)/8.98(p<.0001) PERMP-number correct, F(77.77): 56.24(p<.0001)/6.15(p=.0153)/1.33(p=.2520)/9.97(p<.0001) **Other Measures, MTS vs. placebo** LS Mean SKAMP-D (+/-SE): 3.2 (0.58) vs. 8.0 (0.58), p<0.0001 LS Mean SKAMP-A (+/-SE): 6.2 (0.50) vs. 9.9 (0.50), p<0.0001 ADHD Rating Scale IV: 16 vs. 32, p<0.0001 [estimated from graphic] CPRS-R: 19 vs. 35, p<0.0001 [estimated from graphic] CGI-I: 79.8% vs. 11.6%, p<0.0001 Parent Global Assessment: 71.1% vs. 15.8%, p<0.0001	**MPH vs. placebo, n (%)** Any adverse event: 24 (30.0) vs. 18 (22.5) Headache: 3(3.8) vs. 3(3.8) Anorexia: 2(2.5) vs. 0 Pharyngolaryngeal Pain: 2(2.5) vs. 1(1.3) Rash: 1(1.3) vs. 2(2.5) Nasopharyngitis: 1(1.3) vs. 2(2.5) Nausea: 3(3.8) vs. 0 Rhinitis allergic: 2(2.5) vs. 0 Blood Pressure Increased: 2(2.5) vs. 0 Lymphadenopathy: 2(2.5) vs. 0 Upper Respiratory Tract Infection: 0 vs. 3(3.8)	13/7	Shire Pharmaceuticals	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Michelson 2002	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.	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.	5 day washout	children aged 6-16 years/ 70.6% male, 29.4 female/ ethnicity NR.	**ADHD subtypes** mixed: 60% of placebo, 55.3% of atomoxetine group hyperactive/impulsive: 0% of placebo, 3.5% of atomoxetine group inattentive: 40% of placebo, 41.2 of atomoxetine Co-morbidity trait: placebo vs atomoxetine 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%.	170	3%/NR/ 170

Evidence Table 3. Data abstraction of placebo-controlled trials in children

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

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Michelson 2001 (Good)	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).	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.	NR	mean age 11.2 male: 71% female: 29% ethnicity NR.	Placebo vs Atomoxetine 0.5mg/kg/day vs 1.2 mg/kg/day vs 1.8 mg/kg/day **Total ADHD subtype (%)** Inattentive: 682 (23.1) Hyperactive/impulsive: 197 (6.7) Combined: 2072 (70.2) **Comorbidity (%)** ODD: 31(36.9) vs 21 (47.7) vs 25 (29.8) vs 36 (42.4) Generalized anxiety disorder: 1 (1.2) vs 0 vs 0 vs 0 Depression:0 vs 0 vs 0 vs 1 (1.2) **ADHD subtypes:** Mixed: 67% Hyper-active/impulsive: 2% Inattentive: 31% Unspecified: less than 1%.	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 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
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)	**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.	Lilly	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Michelson 2004	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 1.2mg/kg/day-1.8mg/kg/day for the first 10 weeks then atomoxetine or placebo for 9 months Duration: 9 months	NR	Atomoxetine: n=292 Mean age: 10.6 years 89.4% male Ethnicity: NR Placebo: n=124 Mean age: 10.1 years 90.3% male Ethnicity: NR	Atomoxetine: n=292 ADHD subtype combined: 72.6% hyperactivity/impulsive: 4.5% Inattentive: 22.9% Previous stimulant treatment: 53.8% Comorbid condition oppositional defiant disorder: 42.1% depression: 2.1% generalized anxiety disorder: 2.7% Placebo: n=124 ADHD subtype combined: 74.2% hyperactivity/impulsive: 4.8% Inattentive: 21.0% Previous stimulant treatment: 50.0% Comorbid condition oppositional defiant disorder: 45.2% depression: 1.6% generalized anxiety disorder: 2.4%	604	10/NR/414

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Michelson 2004	Survival curve, proportion not relapsing: atomoxetine>placebo, p<0.001 Atomoxetine baseline: change from baseline vs. placebo baseline: change from baseline *ADHD RS* - 15.8: 6.8 vs 15.7: 12.3, p<0.001 *CGI-S score* - 2.3: 0.9 vs 2.2: 1.4, p=0.003 *CPRS* - oppositional, 6.5: 1.6 vs 5.4: 2.7, p=0.027; cognitive problems, 7.3: 1.9 vs 6.8: 3.7, p<0.001; hyperactivity- 4.5: 1.5 vs 4.6: 3.1, p=0.001; ADHD index, 13.7: 3.7 vs 13.3: 6.9, p<0.001 *CTRS* - all NS *CHQ* - 43.4: -5.6 vs 44.0: -9.5, p=0.016	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	Lilly	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Musten 1997/Firestone 1998 (Fair)	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 disabilities, 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.	methylphenidate 0.3mg/kg or 0.5mg/kg, bid or placebo Duration: 7-10 days for each condition (placebo, low dose, high dose) Timing: NR	NR	Mean age=4.84 years Gender: 83.9% male Ethnicity: NR	Peabody Picture Vocabulary Test (standard score)=99.26(14.41) Diagnostic Interview for Children and Adolescents (number)=12.03(1.49) Swanson 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)	41	4/6/31

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Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
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 %compliance, 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; Cancellation Task rows correct, P<H, L<H, p<0.01	placebo: low dose: high dose (%) Temperament 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 Anxious: 66:72:12, P>H, L>H, p<0.001 Euphoric/unusually happy: 19:25:6, NS Somatic 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 Sociability 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	Health Canada grant 6606-4979-63	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Newcorn 2005	Children and adolescents, 8 to 18 years of age, who met DSM-IV criteria for ADHD by clinical assessment and confirmed by structured interview. Patients were also required to have a symptom severity score ≥1.5 SDs above age and gender norms on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent version, investigator administered and -scored scale (ADHD-RS-IV-Parent:Inv) for either the total score or the Inattentive or Hyperactive/Impulsive subscale scores, corresponding to the combined, primarily inattentive, and primarily hyperactive/impulsive subtypes of ADHD, respectively. Patients were assessed for lifetime psychiatric disorders, including ODD, by clinical history and structured interview, using the K-SADS-PL. Patients with learning disabilities were not excluded. However, patients were required to be of normal intelligence (IQ ≥80) as assessed by either the full WISC-III or the four specified subtests of the WISC-III (Block Design, Picture Arrangement, Similarities, and Vocabulary).	ATX: Fixed dosing of 0.5, 1.2, or 1.8 mg/kg/day or placebo (began treatment at 0.5 mg/kg/day. In the higher dose arms, drug was titrated with intermediate steps of 0.8 mg/kg/day and 1.2 mg/kg/day at 1-week intervals) Mean Dose = NR	NR	Mean Age: 11.1 yrs (Range: 8–18 yrs) Male: 72.5% Ethnicity: NR	ODD vs. non-ODD **ADHD Subtype No.(%) all NS** Hyperactive/impulsive: 5 (2.8) Inattentive: 92 (31.4) combined: 196 (66.9) 115 (39.3%) with ODD 178 (60.8%) without ODD	293	NR/NR/NR

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Newcorn 2005	**1.8 vs. 1.2 vs. 0.5 vs. placebo** **ADHD-RS-IV-Parent Total mean change:** ODD: -13.4 (p=0.030)/-11.5(p=0.092)/-10.8(p=0.185)/-5.1 non-ODD: -13.6 (p=0.050)/-14.9(p=0.009)/-9.1(p=0.690)/-5.1 **ADHD-RS-IV-Parent inattentive mean change:** ODD: -6.9 (p=0.020)/-5.7(p=0.105)/-5.4(p=0.194)/-2.2 non-ODD: -6.8 (p=0.098)/-7.8(p=0.010)/-4.8(p=0.688)/-3.1 **ADHD-RS-IV-Parent hyperactive/impulsive mean change:** ODD: -6.6 (p=0.091)/-5.8(p=0.131)/-5.4(p=0.252)/-2.9 non-ODD: -6.8 (p=0.066)/-7.1(p=0.034)/-4.3(p=0.798)/-3.7 **CGI-ADHD-S mean change:** ODD: -1.2 (p=0.040)/-0.9(p=0.207)/-1.0(p=0.149)/-0.4 non-ODD: -1.3 (p=0.038)/-1.5(p=0.002)/-0.6(p=0.930)/-0.6 **CPRS-R:S, ADHD Index mean change:** ODD: -7.2 (p=0.018)/-6.6(p=0.030)/-7.5(p=0.016)/-0.3 non-ODD: -9.9 (p<0.001)/-10.0(p<0.001)/-7.0(p=0.125)/-2.4 **CPRS-R:S, oppositional mean change:** ODD: -3.4 (p=0.027)/-2.2(p=0.321)/-3.4(p=0.040)/-0.6 non-ODD: -2.3 (p=0.229)/-2.7(p=0.057)/-1.5(p=0.884)/-0.7 **CDRS-R:** ODD: -1.6 (p=0.255)/-1.9(p=0.209)/-1.4(p=0.300)/1.3 non-ODD: -2.2 (p=0.077)/-1.8(p=0.108)/0.6(p>0.999)/0.8 **Measures of QOL** **Psychosocial Summary mean change:** ODD: 10.8(p=0.003)/7.1(p=0.07)/4.4(p=0.238)/-0.4 non-ODD: 7.8(p=<.001)/5.8(p=.006)/4.5(p=0.124)/-0.9 **Behavior mean change:** ODD: 18.6(p=<.001)/13.0(p=.036)/9.1(p=.077)/-2.3 non-ODD: 14.6(p=<.001)/14.0(p=<.001)/7.5(p=0.250)/0.8 **Family Activity Mean Change:** ODD: 16.7(p=.006)/13.9(p=.021)/6.4(p=.269)/-0.9 non-ODD: 14.1(p=.094)/15.7(p=<.054)/10.6(p=0.495)/0.9 **Parent Impact-Emotional Mean Change:** ODD: 7.1(p=.955)/13.0(p=.627)/6.1(p=.269)/8.4 non-ODD: 13.8(p=.023)/9.3(p=.281)/5.4(p=.883)/0.7 **Parent Impact-Time Mean Change:** ODD: 13.0(p=.091)/5.8(p=.313)/2.6(p=.499)/-2.3 non-ODD: 5.8(p=.740)/7.4(p=.637)/1.1(p=.999)/1.3 **Mental Health Mean Change:** ODD: 12.1(p=.017)/7.0(p=.401)/6.4(p=.237)/0.0 non-ODD: 6.5(p=.022)/3.7(p=.086)/8.8(p=.015)/-2.3 **Role-Emotional Mean Change:** ODD: 19.7(p=.071)/8.3(p=.241)/11.6(p=.200)/-5.6	NR	NR; NR	Lilly	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Nolan 1999	Subjects were 19 children (18 boys and 1 girl) between the ages of 6.6 and 17.4 years old who met Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, diagnostic criteria for ADHD and either chronic motor tic disorder or Tourette's disorder (established based on a clinical interview with the parent). To be considered eligible for the study, each child had to be receiving maintenance stimulant drug therapy for a minimum of 1 year. (No attempt was made to determine the total number of days each child actually ingested medication.) In addition, subjects could not be receiving any other medication for ADHD, tics, or other emotional or behavioral disorders.	Methylphenidate: Mean dose = 26mg (SD 10mg) Dose range = 10 - 50mg Dextroamphetamine: Mean dose = NR Dose range = 10mg - 20mg	NR/NR	Mean age=12.3 yrs (SD 3.0 yrs), range 6.6 - 17.4 yrs 95% male Ethnicity: NR	Mean (SD) **Parent ADHD Measures** CGI-3R ADHD category (>7): 10.0 (4.1) CHI (>15): 16.3 (4.7) MOMS Hyperactivity scale (>2): 3.6 (1.3) **Teacher ADHD Measures** CGI-3R ADHD category (>7):10.5 (3.5) CHI (>15): 18.2 (7.7) MOMS Hyperactivity scale (>6): 9.7 (3.0) **Aggression measures** MOMS Aggression scale (>2): 2.0 (1.8) IOWA Aggression scale (>3): 5.5 (4.0) **Clinician Tic measures** YGTSS Motor Tic score:11.6 (3.7) YGTSS Phonic Tic score: 9.4 (4.9) YGTSS Overall Impairment Rating scores: 14.3 (12.7) YGTSS Global Severity score: 35.0 (17.2) Methylphenidate: 17 subjects and Dextroamphetamine: 2 subjects Comorbidities: 100% ADHD and either chronic motor tic disorder or Tourette disorder Tourette disorder: definite=11, by history=7 Chronic motor tic disorder: definite=1	19	NR/NR/19

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Nolan 1999	Placebo (blind) VS. Drug (blind) **Clinician Ratings** **YGTSS** Total Motor Tics: 10.1(7.2) vs. 8.3(4.4) NS Total Phonic Tics: 5.6(5) vs. 3.8(5.3) NS Overall Impairment Rating: 12.1(12.3) vs. 6.8(11.1) NS Global Severity Score: 29(19.5) vs. 19(18.4) NS **STSSS**: 1.6(1.1) vs. 1.5(1.2) NS **TS-CGI**: 2.1(.7) vs. 1.8(.9) NS **TS Unified Rating Scale** Shapiro Symptom Checklist Number of Motor Tics: 4(2.5) vs. 4(4.5) NS Number of Vocal Tics: 1.5(1.6) vs. 1.3(2.2) NS 2-Minute Tic Count Motor Tic Count: 4.3(2.9) vs. 5(4.3) NS Vocal Tic Count: .4(.8) vs. 1.2(1.8) p=.0037 **GTRS** Motor Tic Index: 2.6(1.4) vs. 2.7(1.5) NS Vocal Tic Index: 1.1(1.2) vs. 1(1.4) NS Tic Severity: 1.8(2.3) vs. 1.4(2.2) NS **CGI-OC**: 1.1(.7) vs. 1(.8) NS **Parent Ratings** GTRS Motor Tic Index: 2.5(1.4) vs. 2.9(1.7) NS Vocal Tic Index: 1.5(1.4) vs. 1.2(1.7) NS Tic Severity Index: 2(2.3) vs. 1.8(2.6) NS **Classroom Observations** Motor Tic Frequency: 20.4(13.1) vs. 17.8(13.8) NS Vocal Tic Frequency: 1(3) vs. 1(1.8) NS	none	none	Tourette Syndrome Association; US Public Health Service Grant MH45358; NIMH	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Pelham 1991 (Fair)	Received a primary diagnosis of ADHD	methylphenidate 0.3mg/kg to the nearest 1.25mg, bid or placebo mean dosage: 12.13mg (range 6.25mg-11.25mg) Duration: 4-11 days depending on the child Timing: morning at breakfast and midday	NR	Mean age=12.59 years Gender: 100% male Ethnicity: NR	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 Conners 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)	17	0/0/17
Rugino 2003 (Fair)	(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.	Modafinil mean dose=264 mg Placebo Flexible dosing Dosing schedule=once each morning Mean study duration=5.6 weeks	NR	Mean age=7.9 62.5% male 100% white	ADHD type Combined=72.7% Inattentive=18.2% Hyperactive-impulsive=4.5% Comorbidity: 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%	24	2 (8.3%) withdrawn/0 lost to fu/analyzed=22 (modafinil=11, placebo=11)

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Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
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.	NR	0	NR	
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	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	NR	

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Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Sallee 2009 U.S.	Male and female subjects ages 6 to 17 years with a DSM-IV -TR diagnosis of ADHD and a minimum baseline score of 24 on the ADHD rating scale IV-TR criteria for ADHD and the Kiddie schedule for affective disorders and schizophrenia-present and lifetime diagnostic interview and performed a complete medical history and physical examination.	A. Guanfacine 1mg B. Guanfacine 2mg C. Guanfacine 3mg D. Guanfacine 4mg E. Placebo Treatment period: 9 weeks	NR	Age, Mean (SD), 11 (3) yrs Male: 72% White: 67% Black: 17% Hispanic: 9% Asian or pacific islander: 2.8% Native American: 0.3% Other: 4.3%	ADHD subtype Inattentive: 26% Hyperactive/impulsive: 2% Combined: 73% % of patients with oppositional defiant disorder: 5.6% Mean(SD) ADHD-RS-IV score: 40.1 (8.65)	324	113/ 22/306
Scahill 2001 U.S. (Fair)	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	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	NR	Mean age=10.4 91.2% male 85.3% White 0.6% Black 0.6% Hispanic 0.3% Asian	DSM-IV tic disorders Tourette's: 20 (58.8%) Chronic motor tic disorder: 12 (35.3%) 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	34	NR/NR/34

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Sallee 2009 U.S.	Placebo adjusted mean change from baseline in ADHD-RS-IV score in Guanfacine ER 1mg vs 2mg vs 3 mg vs 4mg -6.75(p=0.0041) vs -5.41 (, p=0.0176) vs -7.34 (p=0.0016) vs -7.88 (p=0.0006) In age group 6-12 yrs, mean weight 84.6 lb: -9.08 (p=0.0007) vs -5.44 (p=0.45) vs -10.29 (p=0.0003) vs -10.77 (p<0.0001) In age group 13-17 yrs, mean weight 130.1lb: -1.06 (p=0.08) vs -5.43 (p=0.2) vs -0.24 (p=0.95) vs 0.26 (p=0.95) Symptoms of inattentiveness: -4.2 (p=0.002) vs -3.0 (p=0.2) vs -3.5 (p=0.007) vs -4.0 (p=0.002) Symptoms of hyperactivity-impulsiveness: -2.7 (p=0.028) vs -2.5 (p=0.03) vs -3.9 (p=0.001) vs -4.0 (p=0.0008) Placebo vs guanfacine ER 1mg vs 2mg vs 3mg vs 4mg(placebo adjusted p-values)) % of patients with GGI improvement (investigator rated): 30% vs 54% (p=0.007)vs43% (p=0.1404) 55% (p=0.006)vs 56% (p=0.004) % of patients with PGA improvement: 30% vs 51% (p=0.030)vs 36%(p=4982) vs 62%(p=0.02)vs 57%(p=0.0063)	Placebo vs Guanfacine ER (all groups combined) Proportion of patients with TEAE: 74% vs 76% Proportion of patients with severe TEAE: 4.5% vs 3.9% Somnolence: 12% vs 27% Headache: 11% vs 21% Fatigue: 3% vs 9% Upper abdominal pain: 9% vs 6% Dizziness: 6% vs 6% Sedation: 5% vs 6% Irritability: 5% vs 6% Nausea: 2% vs 5% Vomiting: 6% vs 3% Nasopharyngitis: 6% vs 2%	Placebo vs Guanfacine ER 1mg vs 2mg vs 3mg vs 4mg Total withdrawals: 37.9% vs 27.4% vs 72.3% vs 58.5% vs 39.4% Withdrawals due to AE: 7.6% vs 3.2% vs 3.1% vs 9.2% vs 13.6%	Shire Development Inc	
Scahill 2001 U.S. (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	Total numbers of subjects reporting adverse events: Mild sedation=7 Mid-sleep 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	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	

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Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Scheffer 2005 U.S.	Study subjects were recruited from a university-based outpatient pediatric psychiatry clinic and the community. Eligible subjects were males and females 6-17 years of age, who met the DSM-IV criteria for both bipolar I or bipolar II disorder (in either the mixed, manic, of hypomanic phase) and ADHD. All subjects had to score >= 14 on the Young Mania rating scale at baseline, to have scores exceeding 2 standard deviations from normal on the hyperactivity index of the Conners' Teachers and Parents Rating Scales, and to be of normal intelligence (IQ>70) on the basis of clinical impression or formal testing.	Adderall 5 mg po bid Placebo 4 weeks of treatment DB (A follow-up of 12 weeks of open label Adderall+divalproex after the 4 weeks of DB also briefly assessed)	Divalproex sodium given concomitantly.	for DB crossover trial only, n=31 Mean age: 9.8 years 83.3% male 93.3% white 6.7% Hispanic	Mean Young Mania Rating score: 28.8 (SD: 5.2) Mixed phase: 83.3% Manic phase: 16.7% Bipolar I: 73.3% Bipolar II: 26.7%	31	1 / NR / 30
Schleifer 1975 (Fair)	Preschool children diagnosed as hyperactive participated in this study	methylphenidate: 2.5 mg - 20mg q AM and 10mg at lunch (mean dose = 5mg bid) Duration: 14-21 days	NR	Mean age=4.08 years Gender: 89.3% male Ethnicity: NR	Mean IQ=102 (86-124) Hollingshead scale (socioeconomic class): Mean=2.5	28	0/2/26

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Scheffer 2005 U.S.	Mean score Adderall (n=14) vs placebo (n=16): At the end of the first 2 week period of the trial, Cgi-I: 1.7 (SD=0.6) cs 3.4 (SD=1.0), p<0.0001 At the end of the 4 week DB trial (i.e., after crossover): 1.8(SD=0.6) vs 3.7 (SD=1.0), p=NR % patients with treatment response according to CGI Improvement Score CGI=1 or 2): 89.6 % on Adderall vs 10 % on placebo	4 week DB phase, which treatment not specified: Abdominal pain n=2 Diarrhea, n=1 Nausea, n=1 Appetite decrease, n=2 Headache, n=1 Drowsiness, n=2 Difficulty falling asleep, n=1 Irritability, n=1 Rash, n=1 AEs not specified for 12 week follow-up period	1 ; NR	Stanley Medical Research Institute	During the 12-week follow-up period (n=23), the average dose was 14.5 mg/day
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	NR	0	Supported in part by a Dominion-Provincial Mental Health grant to Dr. Gert Morgenstern	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Silva 2006	Boys and girls 6–12 years of age who had been diagnosed with ADHD were eligible for enrollment. Patients eligible for inclusion were required to fulfill the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for ADHD of any type, as established by the Computerized Diagnostic Interview Schedule for Children (C-DISC-4). Patients must also have been stabilized on 20–40 mg/day of MPH for at least 1 month prior to screening. Only those patients whose parents and/or guardians provided written, informed consent were enrolled. Assent was also obtained from all children (documented by signature of those older than 9 years).	d-MPH-ER 20 mg/day or placebo	NR/NR	Mean age= 9.4 yrs (SD 1.6) (Range: 6-12 yrs) 70.4% male Ethnicity NR ("predominantly Caucasian")	**DSM-IV ADHD diagnosis N(%)** Inattentive: 5 (9.3) Hyperactive/impulsive: 0 Combined Type: 49 (90.7) **ADHD mean duration, years (SD)**: 4.6 (1.6)	54	1/0/53
Silva 2008 U.S.	Males and females ages 6 to 12 years and diagnosed with ADHD. Al of the subjects had to be clinically and behaviorally stable in the opinion of the referring physician and the site's principal investigator. They also had to have been taking their current dose of medication without adjustment for at least 2 weeks. This was required to be a total daily dose or nearest equivalent of MPH 40 mg or immediate-release D-MPH 20 mg (Concerta 36 mg was allowable) before screening.	Dexmethylphenidate ER 20mg/day Placebo	NR	Mean age: 9.5 years 66.2% male 50% white 22.1% black 0% Asian 19.1% Hispanic 8.8% other	Mean height: 138.2cm Mean weight: 34.4kg Duration of ADHD symptoms: 4.5 years Received medication for ADHD in the past: 100% ADHD combined type: 82.4% ADHD inattentive type: 17.6% ADHD hyperactive-impulsive type: 0%	NR/NR/68	1 withdrew, no lost to follow-up 68 analyzed for safety 67 analyzed for efficacy

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Silva 2006	modafinil vs. placebo SKAMP-Combined scores adjusted mean: -10.014 vs. 0.878, p<0.001 SKAMP Deportment scores, mean change at 12 h postdose: -0.3 vs. 3.6, p=0.001 -estimated from graphic SKAMP Attention score, mean change at 12 postdose: 1.7 vs. 2.6, p=0.046 -estimated from graphic Math—Attempted, mean change at 12 postdose: 20 vs. -11, p< 0.001 -estimated from graphic Math—Correct scores, mean change at 12 postdose: 18 vs. -10, p< 0.001 -estimated from graphic	decreased appetite anorexia: 9.4% vs. 0% fatigue: 3.85% vs. 0% insomnia: 3.85% vs. 0% headache: 1.9% vs. 5.6% irritability: 0% vs. 5.6%	1-Jan	Novartis Pharmaceuticals Corporation	
Silva 2008 U.S.	**Mean change in Scores** SKAMP-Combined - 0.5 hours post-dose: -2.242 (d-MPH-ER) vs 3.493 (Placebo); p=0.001 (8.6% improvement for d-MPH-ER and 66.7% worsening with placebo) - 1, 3, 4, 5, 7, 9, 10, 11, and 12 hours post-dose: d-MPH-ER significantly greater improvement compared to placebo (p≤0.001) SKAMP-Attention - 0.5, 1, 3, 4, 5, 7, 9, 10, 11, and 12 hours post-dose: d-MPH-ER significantly greater improvement compared to placebo (p≤0.001) SKAMP-Deportment - 0.5, 1, 3, 4, 5, 7, 9, 10, 11, and 12 hours post-dose: d-MPH-ER significantly greater improvement compared to placebo (p=0.003 for 0.5 hours, p=0.013 for 12 hours and p≤0.001 for all other time points) Math Test - Attempted: significantly more improvement with d-MPH-ER compared to placebo (p<0.001) Math Test - Correct significantly more improvement with d-MPH-ER compared to placebo (p<0.001)	**d-MPH-ER vs Placebo** Total: 11 (16.2%) vs 11 (16.2%) Upper respiratory tract infection NOS: 3 (4.4%) vs 5 (7.4%) Abrasion NOS: 1 (1.5%) vs 0 Asthma aggravated: 1 (1.5%) vs 0 Folliculitis: 1 (1.5%) vs 0 Gastroenteritis NOS: 1 (1.5%) vs 3 (4.4%) Headache: 1 (1.5%) vs 1 (1.5%) Lymphadenitis NOS: 1 (1.5%) vs 0 Pharyngitis: 1 (1.5%) vs 0 Proteinuria: 1 (1.5%) vs 0 Rhinitis allergic NOS: 1 (1.5%) vs 2 (2.9%) Scabies infestation: 1 (1.5%) vs 0 Toothache: 1 (1.5%) vs 0 Rhinorrhea: 0 vs 1 (1.5%)	1 withdrew due to AE	Novartis Pharmaceuticals Corporation	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Singer 1995	Children with both Tourette's Syndrome and ADHD.	each child started with 1 capsule Clonidine 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	children ages 7.2-13.6 years/ 31 male and 3 female/ 33 Caucasian and 1 African-American	NR	34	3/1/ 34

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Singer 1995	**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 F-Value vs Probability > F-Value** 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	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	Tourette Syndrome Association and US	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Sinzig 2007 Germany	Children and adolescents aged 6–16 years who met diagnostic criteria for ADHD according to the DSM-IV. Teacher ratings on an ADHD-symptom checklist had to be above the 90th percentile.	MPH-MR Initial dose: 20mg Depending on weight and symptoms, medication was titrated up to 40mg or 60mg Weight guidance was as follows: 20-30kg, max 20mg MPH-MR; 31-50kg, max 40mg MPH-MR; >50kg, max 60mg MPH-MR Placebo	NR	MPH group: n=43 mean age: 9.8 years 86.1% male Placebo group: n=42 mean age: 9.8 ears 90.5% male Ethnicity: NR	Duration of ADHD: 5.5 years (MPH) vs 5.2 years (Placebo) DSM-IV Diagnosis of ODD/CD: 58.1% (MPH) vs 71.4% (Placebo)	102/85/85	NR
Sleator 1974 (Poor)	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).	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.	NR	NR	NR	42	NR/NR/28

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Sinzig 2007 Germany	**MPH-MR vs Placebo** ODD/CD Symptom Checklist mean scores at week 4 Teacher - total: 0.31 vs 0.82 (effect size=1.0) Parent - total: 0.80 vs 1.04 Teacher - Part A: 0.41 vs 1.13 (effect size=1.0) Parent - Part A: 1.05 vs 1.34 Teacher - Part B: 0.15 vs 0.36 Parent - Part B: 0.43 vs 0.54 Responders after 4 weeks of treatment: Teacher - total: 23.3% vs 31.0% Parent - total: 51.2% vs 40.5% Teacher - Part A: 23.3% vs 31.0% Parent - Part A: 51.2% vs 40.5% Teacher - Part B: 23.3% vs 47.6% Parent - Part B: 58.1% vs 52.4%	NR	NR	Medice Arzneimittel Putter GMBH & Co	
Sleator 1974 (Poor)	17/42 patients showed deterioration during the placebo month. Of these 17, 5 could not continue receiving placebo for an entire month because their restlessness threatened their successful 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 able 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, post placebo - estimated from graph): Drug-Benefited Group: 8, 17.5, 8.5 Increased Dose Group: 17, 23.8, 14 Remission Group: 7.8, 7.0, 7.7 Mean ASQ for all subjects when receiving medication (placebo eliminated) for Sep, Oct, Nov, Dec, Jan, Feb, Mar, Apr, May: 10, 9.5, 11, 12, 11, 12.5, 11.3, 11.3, 10.8 (estimated from graph)	NR	NR	NIMH grant; MPH supplied by Ciba-Geigy	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Smith 1998/Evans 2001 (Fair)	Adolescents diagnosed with ADHD (DSM-III-R), aged 12 and up, Verbal IQ >80, no conditions that precluded a trial of stimulants.	25, 50 or 75 mg per day methylphenidate or placebo, 3 times per day, during weeks 3-8 of study.	NR	n= 46 mean age= 13.8 yrs 89% male 85% Caucasian	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	46	0/0/46

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
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	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 5.0 vs 1.8; .118 Withdrawn Counselor: 4.1 vs 4.1 vs 7.8 vs 0.7; .001 Parent: 2.2 vs 1.1 vs 1.2 vs 1.6; .909 Stomachache Counselor: 3.0 vs 4.2 vs 4.3 vs 4.6; .804 Parent: 1.5 vs 3.1 vs 3.8 vs 1.5; .005 Ate less than half of lunch Counselor: 19.9 vs 30.4 vs 35.5 vs 12.4; .000 Loss of appetite - Parent: 3.8 vs 8.6 vs 3.9 vs 1.8; .000 Difficulty falling asleep - Parent: 3.3 vs 3.0 vs 3.9 vs 2.3; .269	0	National Institute on Drug Abuse, NIMH, National Institute on Alcohol Abuse and Alcoholism, and the National Institute of Child Health and Human Development	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 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Solanto 2009 U.S.	Age between 7-12 years, concordant reports on the CPRS -L and CTRS-L. For the combined subtype group, T-scores ≥65 on both DSM-IV inattentive and DSM-IV Hyperactive-Impulsive scales; for the predominantly inattentive group, T-scores ≥65 on both DSM-IV Inattentive Scale and <65 on DSM IV hyperactive-impulsive scale. Diagnosis of ADHD, combined or predominantly inattentive according to structured diagnostic interview of the parent DSM-IV version. Expert clinical diagnosis of ADHD, based one review of all information collected, including a clinical interview of the parents to obtain the history and a semistructured clinical interview of the child.	TID dosing regimen A. Low dose IR Methylphenidate 15 mg B. Medium dose- IR Methylphenidate 25 mg C. High dose-IR Methylphenidate 50mg, children<25 kg 35 mg Treatment period: 1 wk crossover study for each drug preceded by a maximum of 2 weeks of open label lead in.	NR	Mean age: 8.8 years Male: 44% Minority representation: 40%	Full scale IQ: 111 ODD: 16% LD: 32% Anxiety: 4% Parent DSM-IV Inattentive scale score : 78 Teacher DSM-IV Inattentive scale score: 69 Parent DSM-IV Hyperactive-impulsive scale score: 69.3 (p=0.003 between two groups predominantly inattentive and combined) Teacher DSM-IV Hyperactive-impulsive scale score: 69.7 (p≤0.001 between two groups predominantly inattentive and combined)	30	5/0/NR

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Solanto 2009 U.S.	Placebo vs methylphenidate low vs medium vs high Change from baseline in ADHD-RS Total score: -6.39 vs -14.58 vs -15 vs 18, p=<0.05 for placebo vs methylphenidate groups Change from baseline in CGI-Severity: -0.52 vs -1.08 vs -1.24 vs -1.44, p<0.05 between placebo vs low dose and high dose, p<0.05 for low dose vs medium dose Change from baseline in Connors' parent inattention scale: -12.19 vs -16.35 vs 16.43 vs -21.03, p<0.05 for placebo, low and medium doses vs high dose Change from baseline in Connors' teacher inattention scale: -6.18 vs -7.94 vs -8.98 vs -9.42, p<0.05 for placebo vs high dose Change from baseline in SKAMP parent inattention scale: -0.81 vs -1.23 vs -1.25 vs -1.39 , p<0.05 for low vs medium and high dose and placebo vs medium and high dose Change from baseline in SKAMP teacher inattention scale: -0.11 vs -0.38 vs -0.81 vs -0.86, p<0.05 for placebo vs medium and high dose	Placebo vs methylphenidate low vs medium vs high dose Change from baseline in side effects total score: -1.04 vs -0.84 vs 0.64 vs 2.44 p<0.05 for placebo vs medium, high dose, p<0.05 for high dose vs placebo, low and medium dose All treatment groups combined Appetite: F=7.996, p≤0.001 Stomachache: F=3.348, p=0.032 Marginal treatment effects on headache: F=2.822, p=0.054 Picks at skin or finger: F=1.059, p=0.053	Overall withdrawal: 16.7% Withdrawal due to AE: 2 (1 low dose treatment vs 1 placebo)	NIMH Grant R21 MH62945	Baseline characteristics reported by conditions: predominantly inattentive and combined mostly

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Spencer 2006	Children and adolescents aged 6 to 17 years with ODD as defined according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria. Key inclusion criteria included normal blood pressure (e.g., within the 95th percentile for their age, height, and sex), an electrocardiographic (ECG) finding within normal range, and no comorbid illness that could affect the efficacy or tolerability of MAS XR.	MAS XR 10, 20, 30, or 40 mg/d or placebo (All doses were given in the morning. Forced-dose-titration design: in which patients randomized to the 10-mg/d group received 1 dose of 10 mg/d for 4 weeks. Patients randomized to the 20-mg/d group received 1 dose of 10 mg/d for the first week and 1 dose of 20 mg/d for the remaining weeks; patients randomized to the 30-mg/d group received 1 dose of 10 mg/d for the first week, 1 dose of 20 mg/d for the second week, and 1 dose of 30 mg/d for the remaining 2 weeks; and patients randomized to the 40-mg/d group received 1 dose of 10 mg/d for the first week, 1 dose of 20 mg/d for the second week, 1 dose of 30 mg/d for the third week, and 1 dose of 40 mg/d for the fourth week.) Mean Dose: NR	bronchodilators and inhaled corticosteroids as needed, also allowed antibiotics and over-the-counter medications that do not affect blood pressure, heart rate, or central nervous system activity./NR	Mean age: 10.6 yrs Male: 69.2% Ethnicity: 70.8% Caucasian 16.2% Black 6.5% Hispanic 6.5% Other	**Pure ODD**: 64 (20.8%) **ODD with comorbid ADHD: 79.2%** **Subtype, No.(% of total)** Hyperactive/impulsive: 17 (5.5) Inattentive: 49 (15.9) Combined: 186 (60.4) Not available: 56 (18.2) **Mean years since ODD diagnosis**: 1.46 (SD=2.5) **Mean years since ADHD diagnosis:** 2.52 (SD=3.3**)** ADHD +ODD: 235 (79.1%) ODD only: 70 (23.6%)	308	46/13/297

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Spencer 2006	MAS XR 40mg vs. 30mg vs. 20mg vs. 10mg vs. placebo **ODD subscale of the (SNAP-IV) teacher rating, mean change (SD):** -0.49 (0.78) vs. -0.46 (0.57) vs. -0.45 (0.91) vs. -0.43 (0.77) vs. 0.09 (0.62) **ODD subscale of the (SNAP-IV) parent rating, LS mean difference:** -0.30 (NS) vs. -0.43(p<0.005) vs. -0.26 (NS) vs. -0.23 (NS) **ADHD subscales of the SNAP-IV parent:** improvements were significant in MAS XR 10mg (p=0.02), 30mg (p=0.002) and 40mg (p=0.009) groups compared with placebo **ADHD subscales of the SNAP-IV teacher:** improvements were significant in MAS XR 10mg (p=0.03), 30mg (p=0.01) and 40mg (p=0.006) groups compared with placebo **CGI-S, % much or very much improved** 61% (p<0.001) vs. 60.9% (p<0.001) vs. 55.4% (p<0.006) vs. 36.2% (p=0.122) vs. 26.7% **CHQ-PF50, change in positive treatment effects for patients treated with MSA XR:** Behavior, p=0.006 Self-Esteem, p=0.04 General health perceptions, p=0.037 Physical summary, p=0.009 Psychosocial summary, p=0.02	**MAS XR 40mg vs. 30mg vs. 20mg vs. 10mg vs. placebo** **No. (%)** Anorexia/Decreased Appetite: 21(34.4)/22(31.9)/22(37.9)/10(16.7)/3(5.0) Insomnia: 17(27.9)/16(23.2)/14(24.1)/8(13.3)/5(8.3) Headache: 16(26.2)/11(15.9)/10(17.2)/11(18.3)/9(15.0) Abdominal Pain: 7(11.5)/10(14.5)/6(10.3)/7(11.7)/3(5.0) Weight Loss: 9(14.8)/8(11.6)/6(10.3)/2(3.3)/0(0), p,0.001 Pharyngitis: 7(11.5)/2(2.9)/3(5.2)/6(10.0)/3(5.0) Nervousness: 5(8.2)/5(7.2)/4(6.9)/3(5.0)/0(0) Emotional Lability: 3(4.9)/6(8.7)/3(5.2)/2(3.3)/1(1.7) Accidental Injury: 4(6.6)/2(2.9)/4(6.9)/1(1.7)/3(5.0)	46/14	Shire Pharmaceuticals	study reports ITT and PP results

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Spencer 2006	Adolescents aged 13 to 17 years, weighing ≤75 kg (≤165 lb), who satisfied DSM-IV-TR 1 criteria for primary diagnosis of ADHD combined subtype (predominantly inattentive subtype or hyperactive-impulsive subtype), were eligible for the study. Key inclusion criteria were an intelligence quotient score ≥80, normal blood pressure (girls--systolic blood pressure, 128-132 mm Hg; diastolic blood pressure, 84-86 mm Hg; boys--systolic blood pressure, 130-140 mm Hg; diastolic blood pressure, 84-89 mm Hg), electrocardiographic (ECG) findings within the normal range, and a willingness and ability to comply with protocol requirements in conjunction with a parent or caregiver. Adolescents who were known to be nonresponsive to stimulants (defined as no clinical improvement after trials of 2 stimulant medications, taken for at least 3 weeks each) or naive to stimulant treatment were eligible for enrollment.	Forced-dose titration MAS XR (10-40 mg/day); Adderall XR vs. placebo MAS XR groups: 10 mg/day MAS XR for 4 weeks 20 mg/day MAS XR (10 mg/day week 1, 20 mg/day weeks 2-4) 30 mg/day MAS XR (10 mg/day week 1, 20 mg/day week 2, 30 mg/day weeks 3-4) 40 mg/day MAS XR (10 mg/day week 1, 20 mg/day week 2, 30 mg/day week 3, 40 mg/day week 4)	NR	Mean age 14.2 years 65.5% male 73.7% white 15.8% black 6.8% Hispanic 3.6% other	78.8% patients were treatment naïve	287	Withdrawn 23; MAS XR 21, placebo 2 Lost to f/u 6 Analyzed 278 Placebo = 52 MAS XR 10 mg/day = 54 MAS XR 20 mg/day = 53 MAS XR 30 mg/day = 58 MAS XR 40 mg/day = 61

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Spencer 2006	Improvement in mean ADHD-RS-IV total scores in all 4 MAS XR groups compared with placebo (p<0.001) at all weeks Mean change from baseline was -17.8 in MAS XR 10 to 40 mg/day groups and -9.4 in placebo group Greater improvements observed in low baseline severity groups for MAS XR 20, 30, and 40 mg/day than placebo (p≤0.01)and in all MAS XR groups with high baseline severity than placebo (p≤0.02) Higher % improved in endpoint CGI-I scale in MAS XR groups than placebo (p<0.01)	MAS XR/ placebo anorexia, decreased appetite 35.6%/ 1.9% headache 16.3%/ 22.2 % insomnia 12.0%/ 3.7% abdominal pain 10.7%/ 1.9% weight loss 9.4%/ 0% 97.5% AEs mild or moderate in intensity	Total withdrawn 23 Withdrawn AE 5 MAS XR, 0 placebo	Shire Pharmaceuticals Inc.	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Spencer 2002	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 Wechsler 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 2mg/kg/day or a total 90mg/day based on therapeutic response and tolerability for 9 weeks	NR/NR	Atomoxetine: Age- mean=9.7 Gender- 98(76%) male Placebo: Age- mean=10 Gender- 103(83%) male Race: NR	Mean IQ: Atomoxetine=103, placebo=106.9, p=0.021 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)	253	59 withdrawn/ 0 lost to fu/ 253 analyzed

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
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	*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%)	Lilly	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Sverd 1992	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.	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	NR	Mean age=8.3(1.96), range 6.1-11.9 years. Gender=11(100%) male Race: NR	Overall Impairment Rating scores from the Yale Global Tic Severity Scale: 2(18.2%): none 4(36.4%): minimal 4(36.4%): mild 1(9.1%): severe Global Severity Scores: mean=40.6(16.6), range 16-79 100% 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%)	11	0/0/0

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Sverd 1992	Placebo vs. 0.1mg/kg; Placebo vs. 0.3mg/kg; Placebo vs. 0.5mg/kg Physician evaluation-- a. YGTSS: NS b. TS unified RS: NS Observations-- a. % on task: 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	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	NR	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Swanson 2006	Male or female patients aged 6 to 17 years who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for ADHD were eligible for enrollment. Additional inclusion criteria included a Clinical Global Impressions-Severity of Illness scale (CGI-S) rating of 4 or higher ("moderately ill" or worse), total and/or subscale cores on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) School Version at least 1.5 standard deviations above norms for the patient's age and gender, an intelligence quotient of at least 80 as estimated by the Wechsler Intelligence Scale for Children-Third Edition, and a score of at least 80 on the Wechsler Individual Achievement Test, Second Edition, Abbreviated. Patients were eligible if they were attending a full-time school (i.e., they were not eligible if receiving home schooling).	Modafinil: Mean Dose: 395 mg Dose Range: 340 mg, 425 mg, or placebo (Titrated during first 7 - 9 days)	NR	Mean age= 10 yrs (Range: 6 - 17 yrs) 71% male 80% white	Modafinil vs. Placebo NS for all between group differences **CGI-S Score, N(%)** Moderately ill:117 (62) Markedly ill: 55 (29) Severely ill: 17 (9) **Current ADHD Subtype, N(%)** Inattentive: 51 (27) Hyperactive/impulsive: 10 (5) Combined: 126 (67) **Previous ADHD treatment N(%)** Total: 104 (55) Methylphenidate hydrochloride: 69 (37) Amphetamine salts: 58 (31) Atomoxetine Hydrochloride: 35 (19) Other: 12 (6) **Patients Receiving Coadministered agents N(%)** Respiratory Agents: 20 (11) Vitamins/nutritional supplements: 5 (3) Nonopioid analgesics/anti-inflammatories: 39 (21) Antihistamines: 11 (6) Anti-infectives: 12 (6) Other: 22 (12) **ADHD-RS-IV total score, mean** School version: 37.5 Home Version: 38.8	190	69/1/183

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Swanson 2006	Modafinil vs. placebo **ADHD-RS-IV School version** Total score: 17.1 vs. 8.2, p<.0001 Inattention: 9.4 vs. 6.6, p<.001 Hyperactivity/impulsivity: 7.7 vs. 2.8, p<.0001 **ADHD-RS-IV Home version** Total score: 13.9 vs. 7.9, p=.001 Inattention: 7.1 vs. 4.0, p<.001 Hyperactivity/impulsivity: 6.5 vs. 3.9, p=.004 **CPRS:R-S** ADHD index: 10.7 vs. 5.2, p<.001 Cognitive problems/inattention: 10.0 vs. 4.1, p<.0001 Hyperactivity: 11.8 vs. 4.6p<.001	**Modafinil vs. Placebo** Insomnia: 30(24) vs. 0(0), p<0.0001 Headache: 21(17) vs. 9(14) Decreased Appetite: 18(14) vs. 1(2), p=0.0042 Infection: 13(10) vs. 10(16) Abdominal Pain: 12(10) vs. 5(8) Fever: 7(6) vs. 2(3) Increased Cough: 7(6) vs. 3(5) Rhinitis: 5(4) vs. 5(8) **AE during the 2-week Observation Period** **Modafinil/Modafinil vs. Modafinil/Placebo vs. Placebo/Placebo** Headache: 2(5)/2(5)/0(0) Abdominal Pain: 1(2)/3(5)/1(3) Contact Dermatitis: 0(0)/2(5)/0(0)	74/12	Cephalon Inc	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Szobot 2008 Brazil	Inclusion criteria were age between 15 and 21 years, male gender, current diagnosis of abuse of or dependence on marijuana or cocaine, current diagnosis of ADHD, and stimulant-naive subjects.	Long acting methylphenidate (MPH-SODAS) Placebo Group A: MPH-SODAS followed by placebo Group B: Placebo followed by MPH-SODAS	NR	Group A Mean age: 17.50 years 100% male 37.5% European-Brazilian Group B Mean age: 17.38 years 100% male 87.5% European-Brazilian	Group A SUD: Marijuana: 100% SUD: Cocaine: 50% SUD: days of cannabis use, last month: 30 SUD: # of cannabis cigarettes per day: 3 Group B SUD: Marijuana: 87.5% SUD: Cocaine: 37.5% SUD: days of cannabis use, last month: 38.57 SUD: # of cannabis cigarettes per day: 2.71 Group A Conduct disorder: 100% ODD: 25% Depression: 12.5% Group B Conduct disorder: 75% ODD: 37.5% Depression: 25% ADHD-combined type: 75% ADHD-inattentive type: 18.75% ADHD-hyperactive/impulsive type: 6.25%	32/29/16	2 withdrew from Group A/none were lost to follow-up/16

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Szobot 2008 Brazil	MPH-SODAS was significantly more effective at reducing ADH symptoms and on subjective functioning compared to placebo, according to both the SNAP-IV and CGI scores ($p \leq 0.001$ for all analyses) No significant sequence or period effect. Baseline SNAP-IV and CGI severity scores were significantly associated with response to treatment ($p \leq 0.001$ for all analyses) No significant differences between treatment, period or order effect in terms of number of days with drug use. However, subjects presented a slight decrease in the number of days with drug use while doses of medication were increased: 5.94 days at 0.3mg/kg/day; 5.87 days at 0.7mg/kg/day; 5.56 days at 1.2mg/kg/day	Treatment with MPH-SODAS significantly reduced appetite ($p \leq 0.001$), no treatment effect was found for insomnia or headache No additional information provided	2 withdrew, 0 for AEs	CNpq (No. 307780/2004-0) and Hospital de Clinicas de Porta Alegre	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Ter-Stephanian 2010 Canada	Children aged 6 to 12 years, diagnosed with ADHD by a psychiatrist or a pediatrician	A. Methylphenidate 0.5mg/kg (adjusted to child's weight) B. Placebo For 1 wk each Crossover trial	NR	8.93 years (SD 1.83) Male: 77.9% Caucasian: 83.8%	Income<$20,000: 34.5% Mean full scale IQ: 97.12 (SD 14.05) Mean DISC IV inattentive symptoms: 7.42 (SD 1.83) Mean DISC IV hyperactive symptoms: 6.14 (2.45) DISC IV total ADHD symptoms: 13.56 (2.86) % of patients with ADHD-Combined subtype: 53.9% % of patients with ADHD-Inattentive symptoms: 33.3% % of patients with ADHD-hyperactive symptoms: 12.7% Children meeting criteria for ADHD combined subtype more likely in boys: x^2 =5.51, df=2, p=0.018 Age difference between 3 ADHD subtype groups: F=9.72, df=2264, p<0.001 Comorbid disorders Anxiety: 47.2% ODD: 40.8% Depression: 7.9%	267	NR/NR/263

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Ter-Stephanian 2010 Canada	Response to Methylphenidate Good responder vs poor responder (CCR rating) % patients: 69.9% vs 30.4% Age, years , mean (SD): 8.79 (1.8) vs 9.2 (1.8), p=0.05 % of boys: 71% bs 29% % of girls: 64.3% vs 35.7% Full-scale IQ, mean (SD): 96.74 (14.6) vs 98.42 (14.46), p=0.4 Household income<$20,000: 78.8 vs 21.2 (p=0.01) ADHD subtypes (p=0.06) Inattentive: 60.2 vs 39.8% Hyperactive: 76.5% vs 23.5% Combined: 73.8% vs 26.2% Children with comorbidity received similar CCR response as those without comorbidity: x^2 : 0.92, df=1, p=0.76 Comorbid disorder and clinical response rating % With comorbidity vs without comorbidity(CCR-rating good responder) Any comorbidities: 71.2% vs 63.6%, p=0.28 ADHD +anxiety disorder: 50.0% vs 71.9%, p=0.02 ADHD +anxiety disorder or depression: 51.7% vs 71.8%, p=0.03 Presence of comorbidity did not predict response to Methylphenidate: OR 1.1.18, 95% CI 0.61 to 2.3), p=0.62 Low income predicted good responders: OR 0.49, 95% CI 0.26 to 0.91, p=0.02 independent of age or sex Presence of ODD or CD in the absence of anxiety disorder or depression did not predict response to Methylphenidate: (OR 1.66, 95% CI 0.89 to 3.11, p=0.11) Presence of anxiety disorder or depression in the absence of ODD or CD was associated with poor responders (OR 0.38, 95% CI 0.17 to 0.85), p=0.02 Anxiety disorder significant predictor of poor responder rating (OR 0.38, 95% CI 0.16 to 0.89), p=0.03 low income predictive of good responders OR 0.48, 95% CI 0.26 to 0.89), p=0.02 independent of age or sex	NR	NR	Canadian Institutes of Health Research and Fonds de la Recherche en Sante du Quebec	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Thurstone 2010 U.S.	Age 13-19 years, ability to understand and provide written, informed parental consent and minor assent if under 18 years old, or individual consent if 18 years or older, diagnosis of ADHD using DSM-IV ADHD checklist score ≥22, DSM IV diagnosis of at least one non-nicotine SUD, plans to live locally for at least 4 mo, willingness to participate in motivational interviewing/cognitive behavioral therapy for SUD	Completer population <u><70kg</u> Atomoxetine, mean (SD), range:1.19 mg/kg (0.19),0 to 1.81mg/kg Placebo, mean (SD), range: 1.29mg/kg (0.16), 1.05 to 1.59mg <u>>70mg</u> Atomoxetine, mean (SD), range:88.8mg(15.0), 62.5 to 100mg Placebo, mean (SD), range: 86.7mg (16.0), 50-100mg Time period: 12 weeks	NR, except it was mentioned that one person took an overdose of bupropion.	Age: 16.1 yrs Male: 78.6% Hispanic/ Latino: 68.6% White: 18.6% Non-white: 81.4% American Indian/Alaska Native: 2.9% Asian: 1.4% African American: 8.6% More than 1 race: 10%	Psychiatric diagnosis Conduct disorder: 52.9% Major depressive disorder: 28.6% SUD diagnoses Alcohol use disorder: 28.6% Cannabis use disorder: 95.7% Nicotine dependence: 57.1% Cocaine use disorder: 2.9% Amphetamine use disorder: 1.4% Hallucinogen use disorder: 1.4% Days of non-nicotine substance abuse: 17.8% Adolescent report ADHD score: 40 Parent report ADHD score: 42.2	70	5/5/unclear

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Thurstone 2010 U.S.	Atomoxetine vs placebo Adolescent self report ADHD score at endpoint, pre-post decrease: 18.19 (95% CI 13.41 to 22.97), p=0.0005 vs 19.02 (95% CI 13.97 to 24.07). p=0.0005. Difference between groups p=0.2975 (study inadequately powered in terms of primary hypothesis). Parent report ADHD score at endpoint, pre-post decrease: 13.82 (95% CI 9.21 to 18.43), p=0.0005 vs 8.82 (95% CI 3.37 to 14.28), p=0.0018. Difference between groups p=0.2654 % of patients with a score of <3 on CGI-I: 53.1% vs 60.6%, x^2 =0.37, p=0.543 Use of non-nicotine substance in the past 28 days , pre-post decrease: 5.78 d (95% CI =2.35 to 9.21), p=0.0013 vs 2.24 d(95% CI -1.18 to 5.67), p=0.1956	Atomoxetine vs placebo SAE:1(2.9%)vs 1 (2.9%) Suicide attempt:0(0%) vs1(2.9%) Seizure:1(2.9%) vs 0(0%) Transient suicidal ideation: 4 (11.4%) vs 7 (20%) Appetite decrease: 21 (60%) vs 13 (37%) Difficult falling asleep: 21 (60%) vs 25 (71%) Difficulty staying asleep: 1818 (51%) vs 21 (60%) Drowsiness: 18 (51%) vs 15 (43%) Vomiting: 18 (51%) vs 7 (20%), p=0.006 Difficulty arising in the morning: 17 (49%) vs 18 (51%) Irritability: 17 (49%) vs 17 (49%) Nausea: 15(43%) vs 11 (40%) Dizziness: 10 (29%) vs 10(29%) Depression: 7(20%) vs 13 (37%) Motor tics (6(17%) vs 5(14%) Tachycardia: 6 (17%) vs 4 (11%)	Atomoxetine vs placebo Total withdrawals: 3(8.6%) vs 2 (5.7%) Withdrawals due to AE: 1 (2.9%) vs 0 (0%)	American academy of child and adolescent psychiatry physician scientist program in substance abuse K12 award (DA 000357-06AK12) and National Institute on Drug Abuse Grants U10 DA013732, DA012845 and 5801DA022284	Not clear if the patient who withdrew due to AE is in addition to numbers lost to follow up. Patients with nausea reported twice in the publication in the AE table with varying numbers.

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Unpublished study 313 US	Children (6-12 years) and adolescents (13-17 years) with ADHD, with a partial response to one of the pre-specified psychostimulants (Adderall XR, Vyvanse, Concerta, Focalin XR, Ritalin LA, Metadate CD, or FDA-approved generic equivalents).	A. Intuniv 1-4 mg/day (mean 3.2 mg/day) + psychostimulants (current stable dose) B. Placebo + psychostimulants (current stable dose) For 9 weeks (5 week dose-optimization period, 3 week dose-maintenance phase)	Allowed medications NR, but reported most frequent concomitant medications: Acetaminophen: 15.7% placebo, 14.0% Intuniv AM, 11.2% Intuniv PM.	Age: 10.8 years 71.6% male White: 67.7% Black or African American: 22% Native Hawaiian/Pacific Islander: 0.7% Asian: 1.3% American Indian or Alaska Native: 0.2% Other: 8.1%	Received methylphenidate products: 53% Received amphetamine products: 47% Received Concerta: 45.3% Received Vyvanse: 29.5% Received Adderall XR: 17.8% Received Focalin XR: 5.9% Received Metadate CD: 1.1% Received Ritalin LA: 0.4% Height: 57.6 inches Weight: 88.43 pounds BMI: 18.27	461	83/17/449 for primary efficacy analysis (455 was the full analysis set and safety population)

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Unpublished study 313 US	Placebo vs Intuniv AM vs Intuniv PM vs All Intuniv (all groups received concomitant stimulant) Change from baseline in ADHD-RS-IV Total Score at Endpoint, LOCF: Mean (SD): -16.0 (11.77) vs -20.4 (12.77) vs -21.0 (12.39) vs -20.7 (12.56) LS Mean: -15.9 vs -20.3 vs -21.2 vs -20.7 Placebo-adjusted difference: LS Mean (95% CI): NA vs -4.5 (-7.5 to -1.4) vs -5.3 (-8.3 to -2.3) vs -4.9 (-7.2 to -2.6) Effect size: NA vs 0.377 vs 0.447 vs 0.412 P-value: NA vs 0.002 vs <0.001 vs <0.001 Placebo vs Intuniv AM vs Intuniv PM: Subgroup Analyses of ADHD-RS-IV Total Score, LS mean change from baseline: Age 6-12 years: -16.7 vs -20.3 (P=0.023) vs -21.8 (P=0.001) Age 13-17 years: -12.3 vs -20.5 (P=0.003) vs -18.6 (P=0.033) Male gender: -15.7 vs -20.3 (P=0.004) vs -21.2 (P=0.001) Female gender: -16.4 vs -19.8 (P=0.199) vs -20.8 (P=0.091) White race: -14.2 vs -18.9 (P=0.003) vs -20.9 (P<0.001) Non-white race: -19.3 vs -23.6 (P=0.085) vs -21.4 (P=0.389) Concomitant methylphenidate: -15.9 vs -21.1 (P=0.006) vs -21.2 (P=0.005) Concomitant amphetamine: -15.9 vs -19.4 (P=0.083) vs -21.0 (P=0.011) CGI-P morning assessment, change from baseline: -6.9 vs -8.4 vs -9.6 vs NR CGI-P evening assessment, change from baseline: -6.0 vs -8.2 vs -8.8 vs NR	Placebo vs All Intuniv doses Headache: 13% vs 21% Somnolence: 7% vs 18% Insomnia: 6% vs 13% Fatigue: 3% vs 10% Abdominal pain: 3% vs 10% Dizziness: 4% vs 8% Decreased appetite: 4% vs 7% Nausea: 3% vs 5% Diarrhea: 1% vs 4% Hypotension: 0% vs 3% Affect lability: 1% vs 2% Bradycardia: 0% vs 2% Constipation: 0% vs 2% Dizziness postural: 0% vs 2% Dry mouth: 0% vs 2% Serious AEs: 0 (0%) vs 2 (0.66%); syncope preceded by nausea and vomiting in one patient, and an episode of self-injurious behavior, worsening aggression, and homicidal ideation in the other. Placebo vs Intuniv AM vs Intuniv PM vs All Intuniv (all groups received concomitant stimulant) Psychiatric Treatment-emergent AEs: Total: 3.3% vs 2.0% vs 2.6% vs 2.3% Aggresion and violent behavior: 3.3% vs 2.0% vs 2.0% vs 2.0% Psychosis/mania: 0% vs 0% vs 0.7% vs 0.3% Suicidal ideation and behavior: 0% vs 0.7% vs 0% vs 0.3%	Placebo vs Intuniv AM vs Intuniv PM vs All Intuniv (all groups received concomitant stimulant) Total withdrawals: 16.2% vs 21.4% vs 16.3% vs 18.9% Due to AE: 0.6% vs 2.6% vs 3.9% vs 3.3%	Shire Pharmaceuticals	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Varley 1983 (Fair)	Patients with long-standing symptoms of impulsivity, short attention span, distractibility and excitability	methylphenidate 0.15mg/kg, 0.3mg/kg, bid Duration: 1 week for each condition (placebo, low dose, high dose) Timing: 8am and 12pm	NR	Mean age=14.27 years Gender: 77.3% male Ethnicity: NR	All subjects had been noted to be stimulant responders. IQ mean=95.91, range 81-128	22	0/0/22
Weiss 2005 International	Children aged 8-12 years with ADHD (any subtype as defined by DSM-IV were eligible. Symptom severity had to be >1.0 standard deviation (SD) above age and sex norms on the ADHD Rating Scale -IV-Teacher Version: Investigator administered and scored (ADHD-RS-IV-Teacher: Inv). Patients were also required to have a mean Conners Parent Rating Scale (CPRS-R:S) ADHD index score at least 1.5 SD above age and sex norms.	Atomoxetine 1.2 to 1.8 mg/kg/d (n=101) Placebo (n=52) 2:1 7-weeks' treatment Mean dose: 1.33 mg/kg of atomoxetine	No	Mean age: 9.9 years 80.4% male Ethnicity: NR	Mean baseline CGI-S score: 4.9 (SD=0.8) Comorbidity: ODD: 33.3% Generalized anxiety disorder: 2.6% Learning disorder: 29.8% Motor skills disorder: 6.5% Communications disorder: 8.1%	153	21 / 3 / 132

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Varley 1983 (Fair)	Dosage effects: Conners' Parent Questionnaire, parent narrative, Conners' Teacher Questionnaire, teacher narrative, all p<0.01 t test for correlated means (Conners/ narrative) <u>Parents</u> -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 <u>Teachers</u> -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	occasional comments regarding sleep disturbance 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	NR	
Weiss 2005 International	Atomoxetine vs placebo: Responders, defined as a 20% reduction in ADHD-RS-IV-Teacher: Inv : 69% vs 43.1%, p=0.003 Responders, defined as endpoint ADHD-RS-IV Teacher:Inv score within 1 SD of the mean for age and sex: 68% vs 51%, p=0.51 Change in scores from baseline: ADHD-RS-IV-Teacher: Inv, Total: -14.5 vs -7.2, p=0.001 Inattentive subscale: -7.5 vs -4.3, p=0.16 Hyperactive/impulsive subscale: -7.0 vs -3.0, p<0.001 CGI-S: -1.5 vs -0.7, p=0.001 CGI-I: +2.6 vs +3.4, p<0.001 Conners Global Index-Teacher: -3.7 vs -0.8, p=0.008 Brown ADD Scale: Teacher: Combined T score: -5.0 vs -2.9, p=0.072 Effort T score: -4.6 vs -1.9, p=0.046 Action T score: -5.7 vs -2.9, p=0.052 APRS, total: +4.8 vs +2.2, p=0.106 Social Skills Rating-Teacher: Problem behavior: -5.3 vs -2.0, p=0.025 Social skills: +4.0 vs +2.4, p=0.196 Conners Parent Rating Scale-Revised Oppositional subscale: -5.4 vs -1.6, p=0.276 Cognitive Problems subscale: -11.8 vs -3.8, p<0.001 Hyperactivity subscale: -12.2 vs -4.2, p<0.001 ADHD Index: -12.1 vs -4.1, p<0.001	Atomoxetine vs placebo: Decreased appetite: 24.0% vs 3.8%, p=0.001 Somnolence: 17.0% vs 3.8%, p=0.020 Change in weight: -0.67 vs +1.21, p<0.001 Change in heart rate: +3.3 bpm vs -0.1 bpm, p=0.67 Vomiting: differences were not statistically significant Discontinuations (n=6) due to AEs in Atomoxetine group were due to: abdominal pain (n=2), emotional disturbance (n=1), feeling abnormal (n=1), irritability (n=1), vomiting (n=1)	21 ; 6 (all in atomoxetine group) 83.2% of atomoxetine patients completed the study (84 of 101) 92.3% of placebo patients complete study (48 of 52)	Eli Lilly and Company	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Wigal 2009 U.S.	Boys and girls aged 6-12 years who satisfied DSM-IV-TR criteria for a primary diagnosis of ADHD, combined or hyperactive-impulsive subtype. Subjects required to have a baseline ADHD-RS-IV score ≥28, age appropriate intellectual functioning as determined by an IQ of ≥80 on the Kaufman Brief Intelligence Test, the ability to complete the PERMP assessment and blood pressure within the 95th percentile for age, gender and height.	A. Lisdexamfetamine 30, 50, 70mg/d B. Placebo 4 weeks dose optimization period followed by 1 wk each of DB crossover treatment	NR	Mean age: 10.1 (SD 1.5) Male: 76% Race Caucasian: 70.5% African American: 13.2% Native Hawaiian or Other Pacific Islander: 0.8% Asian: 0% American Indian or Alaska native: 1.6% Other: 14% Ethnicity Hispanic or Latino: 20.2% Not Hispanic or Latino: 79.8%	Mean ADHD-RS-IV total score at baseline: 42.4 (SD 7.1)	117	18/2/113

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wigal 2009 U.S.	Lisdexamfetamine vs placebo (p-values are vs placebo) LS Mean change from predose in SKAMP-D at 1.5 h post dose: -0.18 vs 0.43, p<0.05, difference in LS Mean, 95% CI -0.45 (-0.62 to -0.28); p<0.0001 LS Mean change from predose in SKAMP-D at 13 hours post dose: 0.17 vs 0.6, p<0.05 difference in LS Mean -0.26, (-0.43 to -0.08), p<0.005 Mean score difference in LS Means , 95% CI -0.74 (-0.85 to -0.63), p<0.0001 LS Mean change from predose in SKAMP total at 1.5 h post dose: 0.53 vs 0.40 , p<0.05 LS Mean change from baseline in SKAMP total at 13 hours post dose: -0.25 vs 0.63, p<0.05 Mean difference in LS Means (95% CI) vs placebo by optimized dose group SKAMP-D 30mg/d, 50mg/d, 70mg/d: -0.70 (-0.88 to-0.52), -0.68 (-0.84 to-0.52), -0.96 (-1.30 to -0.63) SKAMP-Total 30mg/d, 50mg/d, 70mg/d: -0.73 (-0.87 to -0.59), -0.74 (-0.86 to-0.62), -0.99 (-1.24 to-0.74) LS Mean change (SE) from baseline in ADHD-RS-IV total: -25.8 (1.20) vs -8.7(1.20), difference in LS Mean p<0.0001 LS Mean change (SE) from baseline in ADHD inattention: -12.5 (0.62) vs -4.1 (0.62), difference in LS Mean p<0.0001 LS Mean change (SE) from baseline in ADHD hyperactivity/impulsivity: -13.3 (0.64) vs -4.5 (0.64), difference in LS Man p<0.0001 Proportion of patients rated "improved" on CGI scale: 82.3% vs 19.5%, 71.7% improved while receiving treatment not placebo whereas 8.8% where improved while receiving placebo not Treatment p<0.0001	Lisdexamfetamine vs placebo DB phase Proportion of patients with TEAE: 17.4% vs 7.0% Maximum mean(SD) increases from baseline in blood pressure 4.2 (9.2)mm Hg for SBP (70mg lisdexamfetamine at 8 hours post dose), 4.7 (8.5)mm Hg for DBP (70mg Lisdexamfetamine at 8 hours post dose). Maximum mean (SD) increase in pulse 9.9 (9.8)bpm (70mg lisdexamfetamine at 12.5 hours post dose vs 6.6 (12.9)bpm for placebo and 6.6 (13.6) bpm for all active doses of lisdexamfetamine combined Mean (SD) increase in pulse at 8.0 hours post dose 3.5 (13.7) bpm for 70mg lisdexamfetamine vs 4.1 (12.8)bpm for placebo vs 2.6(13.0) bpm for all lisdexamfetamine groups combined.	Lisdexamfetamine vs placebo DB randomization phase Total withdrawals: NR Withdrawals due to AE: 1 vs 0 Withdrawals in the dose optimization +DB phase=18/129 (14% across all doses of lisdexamfetamine) 8 discontinuations occurred before randomization in lisdexamfetamine group.	Shire Development Inc	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Wilens 2006	Adolescent outpatients aged 13 to 18 years having a diagnosis of ADHD (any subtype) were eligible for the study. Diagnosis of ADHD was based on a clinical evaluation using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, confirmed by structured interview (using the behavior module of the Kiddie Schedule for Affective Disorders and Schizophrenia) and by a Children's Global Assessment Scale score of 41 to 70. Eligible subjects could be taking no medications for ADHD at the time of enrollment. Subjects using a behavioral modification program at the time of enrollment had to agree not to change the program or initiate a new program during the study period. Participants had to comply with the study visit schedule, and their parents or caregivers had to be willing to complete all assessments.	methylphenidate, osmotic-release oral system (OROS) 18-72 mg day 11-14 weeks	none	Mean age=14.6 yrs Gender: 80.2% male Ethnicity: 75.1% white 13.6% black 11.3% other	ADHD RS score investigator 31.26 parent 30.82 Parent Child Conflict Index 0.272 Conners-Wells Adolescent Self-report of Symptoms Scale 91.96	220	49/ NR/ 220

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wilens 2006	Change in measures from baseline to end of double blind period of active vs. placebo ADHD RS Investigator -14.93 vs. -9.58 P = 0.001 parent -14.00 vs. -10.14 P = 0.008, Conners-Wells Adolescent Self-report of Symptoms Scale -31.7 vs. -18.7 P= 0.001 and CCI -0.098 vs. -0.016 P= 0.005 CGI-I much or very much improved 51.8% vs. 31.0% P= 0.01	Active vs placebo (%) **headache** 3.4 vs. 6.7 **decreased appetite** 2.3 vs. 0 **insomnia** 4.6 vs. 0 **abdominal pain** 1.1 vs. 2.2 **nausea** 1.1 vs. 2.2 **asthenia** 0 vs. 2.2 **diarrhea** 2.3 vs. 0 for all P = NR	During double-blind phase- Withdrawals active 18% placebo 31% Due to AEs active 1% placebo 0%	McNeil Consumer and & Specialty Pharmaceuticals	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Wilens 2010 U.S.	Children aged 6-12 years with a diagnosis of ADHD by a clinical interview supplemented by a structured psychiatric interview	A. Methylphenidate transdermal 10mg for wk 1, 20mg for wk 2 B. Placebo Cross over trial,2 wk treatment phase for each. Total 4 wks	NR	Mean (SD) age: 9.17 (1.84) Male: 83% Asian American: 3.33% White: 90% More than 1: 3.33% Unknown: 3.33%	Previous treatment: 53% ADHD combined: 53% ADHD Inattentive: 43% Hyperactive/Impulsive: 3% Lifetime comorbidity ODD: 70% CD: 7% MDD:3% Panic disorder:0% Agoraphobia: 17% Social phobia: 10% OCD: 3% GAD: 7% SAD: 30% SUD: 0% Mean past GAF:54.43 (1.91) ADHD-RS score at baseline: 37.80 (9.08) ADHD-AM-RS score at baseline: 30.83 (11.53) Before-school functioning questionnaire: 40.50 (11.64)	unclear	10/NR/30
Wilens 2008 U.S.	Subjects, 6 to 12 years of age, diagnosed with ADHD according to DSM-IV-TR criteria were eligible for the study. Subjects were required to be able to complete the Permanent Product Measure of Performance (PERMP) math test assessment and to have a minimum IQ score of 80. Subjects could not have conduct disorder or comorbid illnesses that contraindicated or could confound MTS treatment.	MPH Transdermal System (MTS) worn for 9 hours (7am-4pm) Initial dose of 10mg, titration up to 15mg, 20mg and 30mg patches Placebo	Investigator monitored concomitant therapies	Mean age: 8.8 years 64.1% male 63.2% white 15.4% black 0% Pacific Islander 0% Asian 0% American Indian 21.4% other	Mean CGI-S score at baseline: 4.8 < moderately ill: 0.9% ≥ moderately ill: 99.1%	148/NR/128	11 withdrew/none lost to follow up/ 117 analyzed

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wilens 2010 U.S.	Methylphenidate vs placebo ADHD-RS-IV score at endpoint: 14.76 (14.48) vs 28.33 (15.75), z=-3.67,p<0.001 Proportion of reduction in ADHD-RS IV score: 61% vs 25% ADHD-AM-RS score at endpoint: 10.03 (13.18) vs 23.22 (14.91), z=-2.94, p=0.003 Proportion of reduction in ADHD-AM-RS score: 67% vs 25% Before school functioning questionnaire score at endpoint: 12.76 (16.65) vs 31.37 (17.79), p<0.01, proportion of reduction: 69% vs 23% Proportion of patients with much to very much improved on CGI-I: 83% vs 30%, x^2: 16.12, p≤0.0001	Methylphenidate vs placebo Loss of appetite: 43% vs 0%, X^2: 12.25, p<0.001 Insomnia: 27% vs 0%, x^2:8.00, p=0.005 Headache: 17% vs 3%, x^2:2.67, p=0.10 Pruritus at site: 13% vs 0%, x^2:4.00,p=0.045	Total withdrawals: 10 Withdrawals due to AE: 2 unclear how many per treatment arm	Shire Pharmaceutical Company	Unclear how many people were randomized. 36 people were screened and 30 completed 1 wk of treatment and eligible for analysis
Wilens 2008 U.S.	SKAMP-Deportment scores averaged over the 4 and 6 hours that the patches were worn during the Analog Classroom sessions were significantly lower for MTS than for placebo (p<0.0001) - Least square mean deportment scores were 11.5, placebo; 5.7, 4-hours after application; 5.9, 6-hours after application SKAMP-Attention scores averaged over the 4 and 6 hours that the patches were worn during the Analog Classroom sessions were significantly lower for MTS than for placebo (p<0.0001) - Least square mean attention scores were 6.3, placebo; 4.0, 4-hours after application; 4.2, 6-hours after application SKAMP-Total scores averaged over the 4 and 6 hours that the patches were worn during the Analog Classroom sessions were significantly lower for MTS than for placebo (p<0.0001) - Least square mean deportment scores were 24.5, placebo; 14.7, 4-hours after application; 15.4, 6-hours after application	326 treatment-emergent AEs were reported 62% were mild intensity and 37% were moderate intensity, only 4 patients (1%) had severe intensity **Most Frequent AEs** Decreased appetite: 28% Headache: 21% Insomnia: 20% Abdominal pain: 12% No serious AEs were reported	11 withdrew, NR how many due to AEs	Shire Pharmaceuticals	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Zeiner 1999 (Fair)	a)boys 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.	Methylphenidate mean dose=22.4mg/day, range 15mg-35mg duration: 3 weeks dosage schedule: NR	NR	Mean age=8.8 years 100% male Ethnicity NR	4 (19%) had developmental reading disorder 5 (24%) showed delayed development of motor functions 13 (62%) was diagnosed as oppositional defiant disorder	21	NR/NR/21

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Zeiner 1999 (Fair)	methylphenidate: placebo PACS hyperactivity- 3.8: 4.5, NS; PACS defiance- 7.4: 11.8, p<0.05 CTRS hyperactivity- 11.2: 16.8, p<0.0001; CTRS defiance- 10.4: 17.6, p<0.0001 CCT commission errors- 1.1: 1.0, NS; CCT omission errors- 2.7: 4.6, p<0.05 CPT commission errors- 4.6: 7.6, NS; CPT omission errors- 7.8: 13.8, p<0.05 PASAT R version- 8.8: 8.4, NS; PASAT S version- 8.2: 7.4, NS MCT dominant hand- 3.9: 12.0, p<0.05; MCT non-dominant hand- 30.8: 35.5, NS GPT dominant hand- 67.7: 74.9, p<0.05; GPT non-dominant hand- 83.7: 91.6, NS RCI showed significant improvement in methylphenidate treatment	NR	NR	Norwegian Medical Research Council, Norwegian Public Health Association, and the Legacy of Haldis and Josef Andresen	

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed
Zeni 2009 Brazil	Age ranging from 8-17 years, diagnosis of bipolar disorder I or II comorbid with ADHD according to DSM-IV criteria, clear report of ADHD symptoms onset preceding any mood symptomatology, at least 30% improvement in mood symptoms in the previous trials of aripiprazole, residual attention, hyperactivity and opposition symptoms defined as a SNAP IV score ≥1.5	A. Aripiprazole+Methylphenidate 0.3mg/kg/d B. Aripiprazole+placebo Treatment period: Crossover trial, 2 weeks each	None	Mean age: 10.71 (1.86) Male: 64.3% Ethnicity: NR	Socioeconomic level A+B+C:92.9% D+E: 7.1% Divorced parents: 57.1% Mean (SD) School grade: 3.14 (1.66) Mean (SD) School repeats: 0.86 (0.95) years Type 1 bipolar disorder: 71.4% Type II bipolar disorder: 28.6% ADHD-inattentive: 7.1% -Hyperactive: 14.3% -Combined: 78.6% Anxiety disorders: 57.1% CD: 57.1% ODD: 78.6% Psychosis: 50% Mean (SD) estimated IQ: 90.96 (12.56) Bipolar disorder (age at onset): 6.5 (2.53) ADHD age at onset: 3.79 (1.93) Baseline scores, Mean (SD) YMRS: 11.14 (9.32) CMRS-P: 16.07 (12.38) SNAP-IV total score: 1.64 (0.53) CDRS-R: 30 (9.97) KADS: 5.43 (3.98) CGI-S: 2.07 (1) AE count: 5.21 (4.98) Barkeley SAERS: 41.64 (25.21) Weight (Kg): 47.7 (15.60)	16	2/1/14

Evidence Table 3. Data abstraction of placebo-controlled trials in children

Author Year Country Trial name Quality rating	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Zeni 2009 Brazil	Mixed treatment model analysis for effects of methylphenidate versus placebo plus aripiprazole SNAP IV total score: $F_{1, 43.22}$=0.00, p=0.97 YMRS: $F_{1,40.90}$=0.93, p=0.34 CDSR-R: $F_{1, 13.15}$=0.41, p=0.54 CMRS-P: $F_{1, 35.46}$=3.08, p=0.09 KADS: $F_{1, 19.03}$, p=0.01 CGI-S: $F_{1, 27.8}$=0.28	Mixed treatment model analysis for effects of methylphenidate versus placebo plus aripiprazole AE counts: $F_{1, 27.07}$=2.61, p=0.12 SAERS: $F_{1, 46.27}$=1.33, p=0.26 Weight: $F_{1, 46.64}$=0.9, p=0.35	Methylphenidate+aripiprazole vs placebo +aripiprazole Total withdrawals: 1 vs 1 Withdrawals due to AE:1 vs 0	Research grant Conselho Nacional de Desenvolvimento Cientifico e Tecnologico Grant 471761/03-6 and Hospital de Clinicas de Porto Alegre(GPPG 03-325)	

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Agarwal 2001	NR	NR	NR	Yes	Yes	Yes	Yes	Yes
Ahmann 2001	NR	NR	Yes	Yes	Yes	Yes	Yes	No
Allen 2005	Yes - computerized interactive voice response system	Yes	Yes, for most characteristics. Higher mean ADHD-RS - IV - Parent: Inv total score and hyperactivity/impulsivity subscale score at baseline in atomoxetine group (described in text; p values not given)	Yes	Unclear, reported as double-blind	Yes	Yes	Yes
Anonymous 2005/Posey 2007	Yes	Yes	No data stratified by treatment group	Yes	Yes	Yes	Yes	No
Arnold 2004	NR	NR	No	Yes	Yes	Yes	Yes	No
Arnold 2006	Method NR	Method NR	Yes, at initial randomization (crossover study)	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes	Yes
Bangs 2007	Method NR	Method NR	No- Mean weight (kg) significantly greater in ATX group: 63.1 vs 58.4; p=0.04	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Unclear, reported as double-blind	1 patient of 142 total excluded from analysis

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Agarwal 2001	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Ahmann 2001	No	*Not rated*	NR NR	Yes No No No	*Not rated*	*Not rated*	Fair
Allen 2005	No	*Not rated*	No	No No No No	*Not rated*	*Not rated*	Good
Anonymous 2005/Posey 2007	No	*Not rated*	No	No N/A No No	*Not rated*	*Not rated*	Fair
Arnold 2004	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Arnold 2006	No	*Not rated*	No	No N/A No No	*Not rated*	*Not rated*	Good
Bangs 2007	No	*Not rated*	No/No: loss to FU 4.2% vs 1.4%, NS	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Bangs 2008	Randomization mentioned, but methods NR	NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes
Barkley 1988	NR	NR	N/A	Yes	Yes	Yes	Yes	Unclear
Biederman 2005	Yes	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes	No
Biederman 2006	Method NR	Method NR	No - due to prespecified randomization procedure, pts randomized to modafinil 400 mg had higher body weight and were older (in text; p values NR)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes	Yes
Biederman 2007	Method NR	Method NR	N/A (crossover study)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind	4% excluded
Biederman 2008	Unclear	Unclear	Yes	Yes	Unclear, described as double-blind	Yes	Yes	No; defined as all patients who had baseline and one followup assessment; number analyzed unclear

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Bangs 2008	8 (5.1%) from Atomoxetine group withdrawn after randomization for protocol violations	*Not rated*	No/No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Barkley 1988	No	*Not rated*	NR NR	No No No No	*Not rated*	*Not rated*	Fair
Biederman 2005	Yes (2 in placebo group)	*Not rated*	No	No No No No	*Not rated*	*Not rated*	Fair
Biederman 2006	No	*Not rated*	No	No No No No	*Not rated*	*Not rated*	Good
Biederman 2007	No	*Not rated*	No/No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Biederman 2008	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Yes, Unclear	No: 130/345 overall (37.7%); reasons for discontinuation differed	Poor

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Bostic 2000	NR	NR	NR	Yes	Yes	Yes	Yes	Yes
Brams 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Brown 1988	NR	NR	N/A	Yes	Yes	Yes	Yes	Unclear
Buitelaar 2007	Yes	NR	Unclear	Yes	Yes	Yes	Yes	No
Casat 1987	NR	NR	Yes	Yes	NR	Yes	Yes	Unclear
Casat 1987	NR	NR	NR	Yes	Yes	Yes	Yes	No; different numbers of patients were excluded from analyses at each time point due to "missing data"
Connor 2010	Yes	Yes	Yes (reported on 214/217 randomized)	Yes	Yes	Unclear, described as double-blind	Yes	Yes; 211/217 analyzed (97.2%)
Connors 1996	NR	NR	Yes	Yes	Yes	Yes	Yes	Unclear
Corkum 2008	Yes	Yes	NR	Yes	Yes	Yes	Yes	7 of 28 excluded (25%)

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Bostic 2000	No	*Not rated*	NR NR	Yes No No No	*Not rated*	*Not rated*	Fair
Brams 2008	No withdrawals reported	*Not rated*	NR/NR	No, NR, NR, NR	*Not rated*	*Not rated*	Fair
Brown 1988	No	*Not rated*	NR NR	No No No No	*Not rated*	*Not rated*	Fair
Buitelaar 2007	Yes	*Not rated*	Yes I: 65/79; C: 54/81	Yes NA No No	*Not rated*	*Not rated*	Fair
Casat 1987	No	*Not rated*	No	NR, NR, NR, NR	*Not rated*	*Not rated*	Poor
Casat 1987	No	*Not rated*	No No	Yes No No No	*Not rated*	*Not rated*	Poor
Connor 2010	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	No; high and differential: overall 60/217 (27.6%); 31/79 placebo (39.2%) vs 29/138 (21.0%) treatment withdrew.	Fair
Connors 1996	No	*Not rated*	Unclear	NR, NR, NR, NR	*Not rated*	*Not rated*	Fair
Corkum 2008	Yes	*Not rated*	No/No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Cox 2006	Yes	NR	NR	Yes	Yes	NA	Yes	NR
Daviss 2001	NR	NR	NR	Yes	Yes	Yes	Yes	Unclear
Dell'Agnello 2009	Unclear	Unclear	Yes on demographics, but differences between groups in diagnoses	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind	Yes; 137/139 analyzed (98.6%)
Dittmann 2011	Yes	Yes (interactive voice response system)	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind	Yes (180/181 analyzed)
Findling 2007	Yes	NR	Yes	Yes	Unclear	Unclear	Yes	NR
Findling 2011	Yes	Yes	Unclear; published report stated that age, gender, ethnicity, race and ADHD subtype distributions were comparable, but data NR; data from clinicaltrials.gov indicate higher proportion of females in LDX 70 mg group (30 mg=24%, 50 mg=20%, 70 mg=43%, placebo=32%)	Yes	Unclear, described as double-blind	Yes, identical appearance of doses	Yes, identical appearance of doses	Yes
Gadow 1992	NR	NR	NR	Yes	Yes	Yes	Yes	Unclear
Gadow 1995	Unclear	No (sealed envelopes)	Unclear; crossover trial; baseline data not reported by group	Yes	Yes	Yes	Yes	Unclear; number analyzed not reported

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Cox 2006	No	*Not rated*	No No	No No No No	*Not rated*	*Not rated*	Poor
Daviss 2001	No	*Not rated*	No	Yes, NR, Yes, NR	*Not rated*	*Not rated*	Poor
Dell'Agnello 2009	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Yes overall: 5/139 (3.6%), but unable to determine if differential.	Fair?
Dittmann 2011	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	No; overall 71.7% completed; dropout rate higher in placebo group (37.3%) due to lack of efficacy	Fair
Findling 2007	4 withdrew (20%)	*Not rated*	No/No	Yes, Yes, NR, NR	*Not rated*	*Not rated*	Fair
Findling 2011	*Not rated*	Yes	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Yes, Yes	Fair
Gadow 1992	No	*Not rated*	Unclear	NR, NR, NR, NR	*Not rated*	*Not rated*	Fair
Gadow 1995	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Unclear, attrition not reported	Poor

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Gadow 2008	Randomization mentioned, but methods NR	Yes	NR	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes	Unclear
Gadow 2011	Unclear	No (sealed envelopes)	Unclear: baseline characteristics reported comparing groups with and without anxiety, not by treatment group	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind	Unclear; no information on attrition
Gau 2007	Yes: Computer-generated random sequence	Yes: Assignment using interactive voice response system	Unclear - typographical error in table makes interpretation difficult; some differences exist	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind	No: Excluded 8 patients (7%)
Geller 2007	Method NR	Method NR	Unclear - some differences, other important parameters not reported	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Unclear, reported as double-blind	Yes, using LOCF
Gonzalez-Heydrich 2010	Unclear (prepared by a statistician)	Unclear (maintained by the research pharmacist)	Unclear; crossover trial; baseline data not reported by group (other than individual patient data on age and gender)	Yes	The PI who evaluated for adverse events was blinded, otherwise unclear, described as double-blind.	Unclear, described as double-blind	Unclear, described as double-blind	Yes - analyzed all who took at least one dose of study medication; unclear how many excluded for not taking any medication
Gorman 2006	Method NR	Method NR	Yes except for concomitant ODD	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes	No

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Gadow 2008	NR	*Not rated*	NR	NR, NR, NR, NR	*Not rated*	*Not rated*	Fair-Poor
Gadow 2011	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Unclear; no information on attrition	Poor
Gau 2007	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Geller 2007	No	*Not rated*	Yes - 0.6% were loss to FU (1 patient in ATX group during placebo run-in), and 25% for all-cause noncompleters	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Gonzalez-Heydrich 2010	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Unclear, attrition not reported	Poor
Gorman 2006	Yes; 2 (one in each group)	*Not rated*	No	No No No No	*Not rated*	*Not rated*	Fair

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Greenhill 2002	NR	NR	Yes	Yes	Yes	Yes	Yes	No
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	Method not reported	Yes	Unclear	Yes	Yes	NA	Yes	No
Greenhill 2006a	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind	No
Greenhill 2006b	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind	No
Grizenko 2006	Method NR	Method NR	Yes, at initial randomization (crossover study)	No	Unclear, reported as double-blind	Unclear, reported as double blind	Yes	Yes
Gross-Tsur 1997	Non-random assignment. Methods for assignment NR	NA	N/A-crossover	Yes	NR	Yes	Yes	Yes
Hall 1972	Yes	Yes	Yes	Yes	Yes	Unclear, reported as double-blind	Yes	Yes
Handen 1990	NR	NR	NR	Yes	Yes	Yes	Yes	Unclear
Handen 1991	NR	NR	NR	Yes	Yes	Yes	Yes	Unclear
Handen 1992	NR	NR	NR	Yes	Yes	Yes	Yes	Unclear

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Greenhill 2002	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Greenhill 2006/Kollins 2006/Wigal 2006 (PATS)	Yes	*Not rated*	Yes Enrolled in crossover titration trial: 165 Enrolled in parallel trial: 114	Yes Yes Yes Yes	*Not rated*	*Not rated*	Fair, despite high attrition (due to extra cautious safety measures).
Greenhill 2006a	No	*Not rated*	No	No No No No	*Not rated*	*Not rated*	Fair
Greenhill 2006b	No	*Not rated*	No	No No No No	*Not rated*	*Not rated*	Fair
Grizenko 2006	NR	*Not rated*	No	No N/A No No	*Not rated*	*Not rated*	Fair
Gross-Tsur 1997	No	*Not rated*	Unclear	NR, NR, NR, NR	*Not rated*	*Not rated*	Poor
Hall 1972	No	*Not rated*	No	No No No No	*Not rated*	*Not rated*	Good
Handen 1990	No	*Not rated*	Unclear	NR, NR, NR, NR	*Not rated*	*Not rated*	Fair
Handen 1991	No	*Not rated*	Unclear	NR, NR, NR, NR	*Not rated*	*Not rated*	Fair
Handen 1992	No	*Not rated*	Unclear	NR, NR, NR, NR	*Not rated*	*Not rated*	Fair

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Handen 1994	NR	NR	NR	Yes	Yes	Yes	Yes	Unclear
Handen 1995	NR	NR	NR	Yes	Yes	Yes	Yes	Yes
Handen 1996	NR	Inadequate - hospital pharmacist	NR	Yes	Yes	Yes	Yes	Yes
Handen 1997	NR	NR	NR	Yes	Yes	Yes	Yes	Unclear
Handen 1999	NR	NR	NR	Yes	Yes	Yes	Yes	No
Handen 2000	NR	NR	NR	Yes	Yes	Yes	Yes	Yes
Hunt 1985	Unclear	Unclear	Unclear; comparison was not made by order of randomization (crossover study)	Yes	Yes, blinded psychiatrists rated videotaped interviews	Yes, "coded tablets"	Yes, "coded tablets"	No; excluded 17% (2/12)
Jain 2011	Unclear	Unclear	Unclear, only reported on 97% of patients (228/236) and more males in clonidine XR 0.2 mg group (78%) than placebo group (68%)	Yes	Yes for parents/guardians, but unclear for investigator - described as double-blind,	Yes, matching tablets	Yes, matching tablets	Yes
Kahbazi 2009	Yes	Yes, pharmacy-controlled	Unclear, only limited demographic information provided	Yes	Yes, raters were blinded	Yes, encapsulated, identical tablets	Yes, encapsulated, identical tablets	Unclear; described use of ITT with LOCF, but actual numbers of patients analyzed NR
Kelsey 2004	NR	NR	Yes	Yes	Yes	Yes	Yes	No
Klein 1988	NR	NR	Yes	Yes	NR	Unblinded study	Unblinded study	No
Klorman 1986/Coons 1986	NR	NR	N/A	Yes	Yes	Yes	Yes	Unclear

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Handen 1994	No	*Not rated*	Unclear	NR, NR, NR, NR	*Not rated*	*Not rated*	Fair
Handen 1995	No	*Not rated*	Unclear	NR, NR, NR, NR	*Not rated*	*Not rated*	Fair
Handen 1996	No	*Not rated*	Unclear	NR, NR, NR, NR	*Not rated*	*Not rated*	Fair
Handen 1997	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Handen 1999	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Handen 2000	No	*Not rated*	Unclear	NR, NR, NR, NR	*Not rated*	*Not rated*	Fair
Hunt 1985	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Yes, Unclear, NR by order of randomization	Fair
Jain 2011	*Not rated*	Yes	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Overall=No (39%) Between-groups=No (placebo=47%, clonidine XR 0.2 mg=31%, clonidine XR 0.4 mg=40%)	Fair
Kahbazi 2009	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Yes, Yes	Fair
Kelsey 2004	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Klein 1988	No	*Not rated*	None	Yes, NR, NR, NR	*Not rated*	*Not rated*	Poor
Klorman 1986/Coons 1986	No	*Not rated*	NR NR	No No No No	*Not rated*	*Not rated*	Fair

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Klorman 1990/Klorman 1991/Klorman 1992	NR	NR	NR	Yes	Yes	Yes	Yes	Unclear
Kollins 2011	Unclear	Unclear	Yes	Yes; but although 31 were screened and not enrolled due to not meeting eligibility criteria, 8 patients were randomized despite having protocol violations.	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind	Yes
Kratochvil 2011	Unclear	Unclear	No; differences in race and ethnicity (more Hispanics and whites in atomoxetine group)	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind	No; 93/101 analyzed (92%)
McGough 2006	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes
Michelson 2001/Biederman 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Michelson 2002/Newcorn 2005	NR	NR	Yes	Yes	Yes	Yes	Yes	No

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Klorman 1990/Klorman 1991/Klorman 1992	No	*Not rated*	NR NR	No No No No	*Not rated*	*Not rated*	Fair
Kollins 2011	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Yes (but lower in placebo group), Unclear	Yes, overall 16.7%; but more in placebo group (22.9% vs 10.7%)	Fair
Kratochvil 2011	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Overall no: 33/101 withdrew (33%); Not differential, except that 6 of atomoxetine vs 2 of placebo excluded from analysis	Poor
McGough 2006	No	*Not rated*	No	No No No No	*Not rated*	*Not rated*	Good
Michelson 2001/Biederman 2002	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Good
Michelson 2002/Newcorn 2005	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Michelson 2004/Hazell 2006	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes
Musten 1997/Firestone 1998	NR	Yes	N/A	Yes	Yes	Yes	Yes	No; analysis excluded 10 patients (24%) - 4 "withdrew" and 6 "did not have completed assessment protocols"
Nolan 1999	Method NR	Method NR	N/A (crossover study)	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes	Unclear
Pelham 1991	NR	NR	N/A	Yes	Yes	Yes	Yes	Unclear
Rugino 2003	NR	NR	Yes	Yes	Yes	Yes	Yes	No, 2 patients excluded
Sallee 2009	Unclear	Unclear	Unclear, no data presented; reports only that no differences at baseline on primary outcome	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Yes	No- defined as patients with baseline and at least one followup assessment.
Scahill 2001	NR	NR	Yes	Yes	Yes	Yes	Yes	Yes
Schleifer 1975	NR	NR	N/A	Yes	Yes	Yes	Yes	Yes

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Michelson 2004/Hazell 2006	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Musten 1997/Firestone 1998	No	*Not rated*	No No	Yes No No No	*Not rated*	*Not rated*	Fair
Nolan 1999	NR	*Not rated*	NR	No N/A No No	*Not rated*	*Not rated*	Fair
Pelham 1991	No	*Not rated*	NR NR	No No No No	*Not rated*	*Not rated*	Fair
Rugino 2003	No	*Not rated*	None	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Sallee 2009	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	No: 113/324 (34.8%) withdrew; reasons differed.	Poor
Scahill 2001	No	*Not rated*	None	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Schleifer 1975	No	*Not rated*	NR NR	No No No No	*Not rated*	*Not rated*	Fair

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Silva 2006	Yes	Method NR	Yes (reported in text; no comparative table)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes	Yes
Silva 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Singer 1995	NR	Yes	NR	No	Yes	Yes	Yes	Unclear
Sinzig 2007	Randomization mentioned, but methods NR	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Sleator 1974	N/A - nonrandomized	N/A - nonrandomized	NR	Yes	NR	Yes	Yes	NR
Smith 1998/Evans 2001	NR	NR	NR	Yes	Yes	Yes	Yes	Unclear
Solanto 2009	Unclear	Unclear	Unclear; crossover trial; baseline data not reported by group	Yes	Unclear, described as double-blind	Yes	Yes	Yes
Spencer 2002	NR	NR	No	Yes	Yes	Yes	Yes	No
Spencer 2005	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double blind	Yes	No for efficacy: 297/308 randomized patients included in efficacy analysis; Yes for safety

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Silva 2006	No	*Not rated*	No	No No No No	*Not rated*	*Not rated*	Fair
Silva 2008	No	*Not rated*	No/No	Yes, Yes, NR, NR	*Not rated*	*Not rated*	Good
Singer 1995	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Sinzig 2007	No withdrawals reported	*Not rated*	NR/NR	No, NR, NR, NR	*Not rated*	*Not rated*	Fair
Sleator 1974	NR	*Not rated*	NR	NR, NR, NR, NR	*Not rated*	*Not rated*	Poor
Smith 1998/Evans 2001	No	*Not rated*	NR NR	Yes No No No	*Not rated*	*Not rated*	Fair
Solanto 2009	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Yes: 5/30 discontinued (16.6%), 3 before receiving any medication, so 2/27 (7.4%) discontinued during treatment, one active treatment, one placebo.	Fair
Spencer 2002	No	*Not rated*	NR	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Spencer 2005	No	*Not rated*	No	No No No No	*Not rated*	*Not rated*	Good

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Spencer 2006	Method not reported	NR	Unclear	Yes	Unclear, although says "double-blind" in title	Unclear, although says "double-blind" in title	Unclear, although says "double-blind" in title	Yes
Sverd 1992	NR	NR	NR	Yes	Yes	Yes	Yes	Unclear
Swanson 2006	Method NR	Method NR	Yes	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes	Yes
Szobot 2008	Randomization mentioned, but methods NR	Yes	Yes	Yes	No	No	Yes	Yes
Ter-Stepanian 2010	Unclear	Unclear	Unclear; crossover trial; baseline data not reported by group	Yes	Unclear, described as double-blind	Yes	Yes	Unclear; no information on attrition
Thurstone 2010	Unclear	Yes, research pharmacist	Unclear; atomoxetine group had higher proportion white (31% vs 6%; P=0.006) and fewer numbers of non-nicotine SUD diagnoses	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind	Yes

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Spencer 2006	Yes	*Not rated*	No No	Yes NA Yes No	*Not rated*	*Not rated*	Fair
Sverd 1992	No	*Not rated*	Unclear	NR, NR, NR, NR	*Not rated*	*Not rated*	Fair
Swanson 2006	Yes (1 patient in modafinil group)	*Not rated*	No	No No No No	*Not rated*	*Not rated*	Fair
Szobot 2008	No	*Not rated*	No/No	Yes, Yes, NR, NR	*Not rated*	*Not rated*	Fair
Ter-Stepanian 2010	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Unclear, attrition not reported	Poor
Thurstone 2010	*Not rated*	Yes	*Not rated*	*Not rated*	Unclear, Yes, Unclear	Yes, Yes	Fair

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Unpublished study 313	Unclear; no details provided about methods	Unclear; no details provided about methods	Unclear; somewhat lower weight in guanfacine PM group (placebo=89.14 lbs, guanfacine AM=90.76 lbs, guanfacine PM=85.40 lbs);more patients were on atomoxetine and dexamphetamine in the placebo group (10.5 and 39.2 %, respectively) than in the Intuniv AM (8 and 33.3 %, respectively) and PM (7.9 and 34.9 %, respectively) groups prior to entering the study; no comparison of ADHD history or severity	Yes	Unclear; described as double-blind, but no information provided about blinding of outcome assessors	Yes; described as double-blind and used matching placebo	Yes; described as double-blind and used matching placebo	Yes, only excluded 12 (3%) who did not take medication or did not have post-baseline data
Varley 1982	NR	NR	NR	Yes	NR	Yes	Yes	Yes
Varley 1983	Yes	NR	N/A	Yes	Yes	Yes	Yes	Yes

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Unpublished study 313	N/A	N/A	N/A	N/A	Unclear, Unclear, Unclear	Yes; Unclear	Fair
Varley 1982	No	*Not rated*	No/No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Varley 1983	No	*Not rated*	No No	Yes No No No	*Not rated*	*Not rated*	Fair

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Wigal 2009	Unclear	Unclear	Unclear; comparison was not made by order of randomization (crossover study)	Yes	Unclear; blinding of outcome assessors NR, but described as double-blind	Unclear; success of masking analysis NR; use of 4-week, open-label, dose-optimization phase may have increased risk that patients could guess treatment assignment during DB phase	Unclear; success of masking analysis NR; use of 4-week, open-label, dose-optimization phase may have increased risk that patients could guess treatment assignment during DB phase	Yes, only excluded 3.4%
Wilens 2006	Yes	Yes	Yes, except more males in C vs I	Yes	Yes	NA	Yes	Yes
Wilens 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wilens 2010	Unclear	Unclear	Unclear; comparison was not made by order of randomization (crossover study)	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind	No, excluded 17% who completed less than a week of treatment
Zeiner 1999	NR	NR	NR	Yes	Yes	Yes	Yes	Yes
Zeni 2009	Unclear	Yes; independent third party	Unclear; comparison was not made by order of randomization (crossover study)	Yes	Unclear for clinicians, yes for parents	Yes, matching placebo	Yes, matching placebo	No, excluded 2/16 (12.5%) who did not complete the trial

Evidence Table 4. Quality assessment of placebo-controlled trials in children

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality Rating
Wigal 2009	*Not rated*	Unclear (unclear at baseline)	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Yes for overall; Yes for between-group based on attrition after randomization: 30 mg=4%, 50 mg=6%, 70 mg=5%	Fair
Wilens 2006	Yes	*Not rated*	Yes I: 16/87 C: 28/90	Yes NA Yes No	*Not rated*	*Not rated*	Good
Wilens 2008	No	*Not rated*	No/No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Good
Wilens 2010	*Not rated*	Unclear (unclear at baseline)	*Not rated*	*Not rated*	Unclear, Yes, Unclear	Overall=No (28%) Between-groups=Unclear, not reported by order of randomization	Poor
Zeiner 1999	No	*Not rated*	No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Zeni 2009	*Not rated*	Unclear (unclear at baseline)	*Not rated*	*Not rated*	Unclear, Yes, Unclear	Overall=yes; Between-groups=Unclear, not reported by order of randomization	Fair

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Adler 2009 "Once daily atomoxetine…" U.S. (Fair)	Adults aged 18-54 years who met DSM-IV text revision (DSM-IV-TR) criteria for adult ADHD as assessed by CGI-ADHD-S score of 4 or higher , had AISRS symptom checklist score that did not change by more than 25% between visits 1 and 2 and had impairment due to ADHD symptoms in the home setting as indicated in the diagnostic interview were eligible to participate.	A. Atomoxetine 25 -100mg/d, mean modal dose 83.9mg/d B. Placebo Time period: 6 months	NR	Mean age: 37.6 years Male: 50% White: 87.9%	Combined subtype (Inattentive and hyperactive impulsive): 72%

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Adler 2009 "Once daily atomoxetine…" U.S. (Fair)	501	295/NR/488	Atomoxetine vs placebo (LOCF analysis), p values are vs placebo Mean (SD)change from baseline in AISRS total score at 6 months: -14.1 (13.3) vs -10.5 (12.7) p<0.001 Mean (SD) change from baseline in AISRS hyperactive/impulsive at 6 months: -6.1 (6.9) vs -4.8 (6.7), p=0.039 Mean (SD) change from baseline in AISRS inattentive score at 6 months: -8.0 (7.4) vs -5.7 (6.9), p<0.001 Mean (SD)change from baseline in CGI-ADHD-S score at 6 months: -1.2 (1.2) vs -0.9 (1.2), p=0.010 Mean (SD)change from baseline in AAQoL total at 6 months: 13.1 (16.1) vs 8.6 (16.9), p=0.005

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Adler 2009 "Once daily atomoxetine…" U.S. (Fair)	Atomoxetine vs placebo (p-values are vs placebo) 6 mo time point Nausea: 32% vs 9%, p<0.001 Headache:16% vs 16%, p=0.902 Fatigue: 16% vs 8%, p=0.011 Decreased appetite: 14% vs 3%, p<0.001 Insomnia: 10% vs 9%, p=0.876 Dizziness: 10% vs 4%, p=0.033 Somnolence: 6% vs 4%, p=0.426 Weight loss for atomoxetine treated patients at 6 mo: 1.6kg, p<0.001 Increase in diastolic blood pressure: 1.2mm Hg vs 0.5mmHg, p=NS Increase in pulse rate: 3.8bpm vs 1.5bpm, p<0.001 10 wk time point Nausea:29% vs 8%, p<0.001 Headache: 15% vs 14%, p=1.00 Fatigue:14% vs 7%, p=0.013 Decreased appetite:13% vs 3%, p<0.001 Insomnia:9% vs 8%,p=0.874 Dizziness:8% vs 4%, p=0.134 Somnolence:6% vs 4%, p=0.310 Weight loss for atomoxetine treated patients at 10 wk time point: 1.3 kg, p<0.001 Increase in diastolic blood pressure: 1.7mm Hg vs 0.2mmHg, p=0.02 Increase in pulse rate: 4.5bpm vs 0.4bpm, p<0.001	Atomoxetine vs placebo Total withdrawals: 62.4% vs 55.4% Withdrawals due to AE: 17.2% vs 5.6%, p<0.001	Eli Lilly and Company	

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Biederman 2010 U.S. (Fair)	Adult outpatients with ADHD between 19-60 years of age. Patients had to satisfy full diagnostic criteria of ADHD based on DSM-IV with childhood onset and persistent symptoms based on clinical assessment and confirmed by structured diagnostic interview and an adult ADHD investigator symptom rating scale (AISRS) score of 24 or higher. Subjects treated for anxiety disorders or depression who were on a stable medication regimen for at least 3 months and who had a disorder-specific CGI-S of 3 or lower (mildly ill) were included	Phase 1 A. OROS Methylphenidate mean daily dose 78.4 (31.7)mg B. Placebo mean daily dose 96.6 (26.5) Time period 6 weeks Phase 2 Responders from phase 1 Treatment period 6 mo Phase 3 MPH OROS responders randomized to active medication or placebo Treatment period 4 weeks		Mean age: 35 years Female:60%	Hamilton anxiety score: 3.8 Hamilton Depression score: 4.2

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Biederman 2010 U.S. (Fair)	Phase 1:227 Phase 2: 96 Phase 3: 23	184(phase 1 and 2)/NR/223 Phase 1, 96 phase 2, 23 phase 3	OROS Methylphenidate vs placebo 6 wk acute phase Proportion of patients reaching responder status at endpoint (CGI≤2 and AISRS improvement>30%: 62% vs 37%, p<0.001 Change from baseline in Hamilton Anxiety: -1.1 vs -1.0, p=0.9 between groups Change from baseline in Hamilton Depression: -1.0 vs -1.0, p=0.9 between groups 24 wk DB phase Proportion of patients with relapse in 24 wk DB phase (CGI deterioration ≥2 points or decline in improvement in AISRS to below 15%): 18% vs 18%, p=0.9 Change from baseline (wk 6) in ADHD symptom score: OROS methylphenidate (p=0.4) or placebo (p=0.3) Phase 3 DB discontinuation phase Time by treatment interaction term for AISRS(p=0.009) reflects decrease in symptoms in OROS Methylphenidate group and increase in placebo Rate of relapse between OROS Methylphenidate responders randomized to placebo vs continuing active treatment: 18% vs 0%, p=0.1

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Biederman 2010 U.S. (Fair)	OROS Methylphenidate vs placebo Increased appetite: Phase 1: 0% vs 0%, Phase 2:2% vs 0%, Phase 3: 0% vs 0% Decreased appetite: Phase 1:24% vs 6%, p<0.05 vs placebo Phase 2 27% vs 3%,p<0.05 vs placebo, Phase 3: 17% vs 9% Headache: Phase 1:27% vs 20%, Phase 2: 52% vs 38%, Phase 3: 33% vs 27% Insomnia: Phase 1:11% vs 4%,p<0.05 vs placebo Phase 2: 19% vs 3%, p<0.05 vs placebo, Phase 3: 33% vs 9% Cardiovascular: Phase 1 4% vs 3%, Phase 213% vs 3%, Phase 3: 17% vs 9% Agitated/Irritable: Phase 1:6% vs 5%, Phase 2: 19% vs 6%, Phase 3: 25% vs 9% Dizzy/Lightheaded: Phase 1:5% vs 3%, Phase 2:6% vs 0%, Phase 3: 0% vs 0%	OROS Methylphenidate vs placebo Phase 1 Overall withdrawal: 42% vs 70% Withdrawal due to AE: 11% vs 3%, p=0.01 Phase 2 Overall withdrawal: 58% vs 61.8% Withdrawal due to AE: 21% vs 3%, p=0.02	Ortho McNeil Janssen Scientific Affairs, LLC	

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Brown 1985	40 boys whose parents and teachers agreed that he demonstrated, in serious and persistent form (symptoms demonstrated 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.	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"	No	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, NS.; these results indicate equality prior to treatment between subgroups.

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Brown 1985	40	NR/NR/40	F ratios determined using separate MANOVAs to determine differences in the effectiveness of treatment and to determine the persistence of each treatment at delayed post-testing (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 Commissions: 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 significant, but differences betweer posttest and DPT were ns (no p-value given). Canonical correlation coefficients (Rc2) for the multivariate analyses for MPH Only; Combined; CTO 0.963; 0.971; 0.926 (amount of variance in dependent measures across pre-, post-, and DPT accounted for by the differences in MPH only and Combined treatments was virtually the same).

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Brown 1985	NR	NR	NR	

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
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 Perceptual 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, variability among subscores on WISC of 6 or more points	n=68 randomized into 1 of 4 groups: Group A: placebo/no tutoring (n=18) Group B: placebo/tutoring (n=17) Group C: dextroamphetamine/no tutoring (n=17) Group 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.	NR	NR NR NR	NR

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Conrad 1971 (Poor)	68	NR	**Mean difference scores between baseline and post-testing** reported as variable: Group A (placebo/no tutor); Group B (placebo/tutor); Group C (dextroamphetamine/no tutor); Group 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 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Conrad 1971 (Poor)	NR	NR	NY State Department of Mental Hygiene Contract No. C36725	

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
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.	Subjects randomly assigned to one of three groups: 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 problematic behavior and absence of negative side effects), average dose was 22 mg/day. Duration: 24 months. Dosing schedule NR.	NR	ages: 5-9 yrs gender: NR ethnicity: NR	NR

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Firestone 1986	73	NR/ 21 lost to FU/ 52 analyzed for entire 2 yr period	**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 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Firestone 1986	NR	NR	Ontario Ministry of Health grants	

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Ialongo 1993 (Fair)	Children had to meet DSM-III-R criteria for ADHD, based on a) Conners Parent and Teacher Hyperkinesis 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.	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	No	Average Age = 8.27 years Male = 77.4% White = 84.9% African-American = 9.4% Hispanic = 3.8% Asian American = 1.9%	Original study of n=107: Conduct disorder: 7.5% (n=8) Oppositional defiant disorder: 43.0% (n=46)

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Ialongo 1993 (Fair)	96	18/7/71 analyzed	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 posttest to FU contrasts were significant for medication by period effect: pretest to post-test: F[4,120]=5.05, p=0.001; posttest to FU: F[4,121]=3.37, p=0.012 Univariate Fs for off-task behavior: pretest to post-test: F[2,62]=10.36, p<0.001; posttest to FU: F[2,60]=7.18, p=0.002 -Children receiving stimulant medication showed a significantly greater deterioration 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 improvement from pre-test 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 children receiving PT+SC+medication. (no data given).

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Ialongo 1993 (Fair)	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	NR	

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Kupietz 1987 (Fair)	Children between 7 and 13 inclusive, 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.	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	NR	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

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Kupietz 1987 (Fair)	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	Conners TRS scores with the adjusted means for Aggressiveness (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 groups 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 weeks 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 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kupietz 1987 (Fair)	NR	11 withdrawals; study states that some withdrew due to side effects, but does not give a specific number	NIMH grant MH 36004	

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
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.	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 maintenance dose. -MM and CT subjects originally given MPH: 77.3% (n=198 of 256 who completed titration) MM and CT subjects originally given Dex: 10.2 % (n=26) MM and CT subjects originally given no medication: 12.5% (n=32) average initial dose of MPH = 30.5 mg/day -At the end of 14 months, MM and CT subjects taking MPH: 73.4% (n=212 of 289 completing both MM and CT) MM and CT subjects taking Dex: 10.4% (n=30) MM and CT subjects on other drugs: 3.1% (n=9) MM and CT subjects on no medication: 13.1% (n=38) CT subjects received 31.2 mg of MPH versus MM=37.7 mg of MPH by treatment end point -At the end of 14 months, CC subjects taking MPH: 57.5% (n=84 of 146 CC subjects) CC subjects taking Dex: not specified CC subjects on other drugs: 16.4% (n=24) CC subjects on no medication: not specified Mean total daily dose for CC subjects=22.6 mg of MPH at treatment end point 14 Month Duration for all treatment arms	NR	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% 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)

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
MTA Cooperative Group 1999, 2004	579	NR/NR/526 analyzed (number gotten from test score subject numbers at 14 months)	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 achievement 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 significant (p=0.016) for ODD symptoms 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 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
MTA Cooperative Group 1999, 2004	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 server side effects (depression, worrying, or irritability) could have been due to non-medication factors)	20 complete dropouts by 14 months = 3.5%; Withdrawals due to AE's: not specified	NIMH grants	

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Young 2011 U.S. (Fair)	Adults aged 18 and older meeting DSM-IV-TR criteria for adult ADHD, having a historical diagnosis of ADHD during childhood both assessed by Conners' Adult ADHD diagnostic interview for DSM-IV. CGI-ADHD-S score of ≥4 and meeting family unit criteria	A. Atomoxetine on-label titration 40g/d for 3 days followed by 80mg/d for wk 1 and 2 max dose 100mg/d B. Atomoxetine slow titration 40mg/d for 7 days followed by 80mg/d for wk 1 and 2 , max dose 100mg/d C. Placebo Mean final atomoxetine dose90.3mg/d, mean modal dose 88.6mg/d DB Treatment period=24 weeks plus 2 wk DB titration period for placebo patients initiating atomoxetine treatment	NR	Age: 41.3 Male: 47.6% White: 84.9%	Weight: 86.6 kg ADHD subtype combined: 68.7% Inattentive: 31.1% Hyperactive-impulsive: 0.2% Previous stimulant exposure: 16.3% Mean CAARS-Inv:SV total ADHD symptom score: 35.0 Mean CGI-ADHD-S score: 4.6

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Young 2011 U.S. (Fair)	502	249/54/496	Atomoxetine vs placebo (p values are vs placebo) Mean (SD)Change from baseline in CAARS total ADHD symptom score at 24 weeks: -14.3(11.8) vs -8.3 (11.0),, effect size:0.57 p<0.001, on-label and slow titration group superior to placebo p<0.0001, difference between on-label and slow titration group=NS Inattention subscale: -8.1 (6.9) vs -4.4 (6.4), p<0.001 Hyperactivity-impulsivity subscale: -6.2 (6.0) vs -3.9 (5.8), p<0.001 % of patients meeting response criteria 25% decrease from baseline in CAARS score at 24 weeks: 68.2% vs 41.8%, p<0.001 % of patients meeting response criteria 50% decrease from baseline in CAARS score: 47.3% vs 27.6%, p<0.001 Mean (SD)Change from baseline in AISRS total score at 24 weeks: -13.7 (12.5) vs -8.0 (11.0), p<0.001 Inattentive score: -7.6 (7.0) vs -4.4 (6.3), p<0.001 Hyperactivity score: -6.1 (6.6) vs -3.7 (5.8), p<0.001 Mean (SD) change from baseline in CGI-ADHD-S at 24 weeks: -1.2 (1.2) vs -0.7 (1.0), effect size=0.46, p<0.0001 Mean (SD) change from baseline in MADRS total score at wk 24: -0.6 (6.5) vs -0.4 (6.2), p=0.797

Evidence Table 5. Data abstraction of long-term efficacy trials

Author Year Country Trial name Quality rating	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Young 2011 U.S. (Fair)	Atomoxetine vs placebo Proportion of patients reporting 1 or more AE: 93.2% vs 81.6% Proportion of patients reporting SAE: 1.5% vs 1.3% Nausea: 34.2% vs 7.3%, p<0.001 Decreased appetite: 19.9% vs 4.3% p<0.001 Headache: 19.5% vs 24.4%, p=0.232 Insomnia: 12.8% vs 5.6%, p=0.006 Fatigue: 13.5% vs 8.5%, p=0.089 Dizziness: 11.3% vs 4.3% Irritability: 9.4% vs 8.1%, p=0.639 Somnolence: 8.6% vs 3.8%, p=0.042 Vomiting: 5.6% vs 2.6%, p=0.117 Upper abdominal pain: 5.3% vs 0.9%, p=0.005	Atomoxetine vs placebo Total withdrawals: 55.6% vs 42.7% Withdrawal due to AE: 25.2% vs 9.4%	Lilly, USA, LLC	

Evidence Table 6. Quality assessment of long-term efficacy trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
Adler 2009 (Once-daily atomoxetine…)	Yes, computer algorithm	Yes, interactive voice response system	Unclear, declared no differences, but table of characteristics not provided	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind	Yes, LOCF
Biederman 2010	Unclear	Yes, pharmacy-administered	Unclear; only limited data provided on age, sex, HAM-A, and HAM-D provided for phase I	Yes	Yes, "Physician raters and subjects were equally blind to treatment assignment"	Yes, identical tablets	Yes, identical tablets	Yes for phase I
Brown 1985	NR	NR	NR	Yes	NR	No	No	NR
Conrad 1971	NR	NR	NR	Yes	Yes	Yes	Yes	No
Firestone 1986	NR	NR	NR	Yes	Yes	Yes	Yes	No
Ialongo 1993	NR	NR	No, more non-white children in placebo group	Yes	Yes	Yes	Yes	Yes
Kupietz 1987	NR	NR	NR	Yes	Yes	Yes	Yes	No, sample size varied across dependent measures, based on incomplete data

Evidence Table 6. Quality assessment of long-term efficacy trials

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality rating
Adler 2009 (Once-daily atomoxetine…)	*Not rated*	Yes	*Not rated*	*Not rated*	Unclear, Unclear (> 75% had 70% adherence), Unclear	Overall=No (41%) Between-group=Yes	Fair
Biederman 2010	*Not rated*	Yes for phase I	*Not rated*	*Not rated*	Unclear, Unclear, Unclear	Phase I: Yes, Yes Phase II: No (60%), Yes Phase III: Unclear, Unclear	Fair for phase I
Brown 1985	NR	*Not rated*	NR	NR, NR, NR, NR	*Not rated*	*Not rated*	Poor
Conrad 1971	NR	*Not rated*	No/No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Poor
Firestone 1986	No	*Not rated*	NR	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Ialongo 1993	No	*Not rated*	No/No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair
Kupietz 1987	No	*Not rated*	No/No	Yes, NR, NR, NR	*Not rated*	*Not rated*	Fair

Evidence Table 6. Quality assessment of long-term efficacy trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intention-to-treat (ITT) analysis
MTA Cooperative Group 1999, 2004	NR	Yes	No, significant differences across treatment groups in age	Yes	Yes	No	No	No
Young 2011	Yes	Yes, telephone voice response system	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, reported that all patients with a baseline and at least 1 post-baseline CAARS-Inv:SV Total ADHD Symptom score was included in primary efficacy analysis using LOCF, but actual N analyzed NR

Evidence Table 6. Quality assessment of long-term efficacy trials

Author, Year Country	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? *(Update 4)*	Quality rating
MTA Cooperative Group 1999, 2004	No	*Not rated*	NR	Yes, Yes, Yes, Yes	*Not rated*	*Not rated*	Fair
Young 2011	*Not rated*	Unclear	*Not rated*	*Not rated*	Unclear Yes, except week 4 when compliance was greater for placebo Unclear	Overall: No=49% Between-group: No=atomoxetine=56%, placebo=43%	Fair

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Adler 2008 (Atomoxetine) US	Ages 18-50 years old who met DSM-IV criteria for current ADHD and a historical childhood diagnosis of ADHD; have a severity of at least 4 (moderate) on the Clinician Global Impressions Severity Scale; employed 20/per week for 6 months prior to study.	Atomoxetine vs placebo Atomoxetine or placebo titrated from 40 mg to 80 mg per day. Dose flexible from 40 mg to 100 mg / day based on tolerability. Treatment phase = 6 months open-label extension phase = up to 4 months	NR	Mean age 36.5 59.7% male 81.8% Caucasian 8.6% Hispanic 6.2% African American 1.25% Asian 2.2% Other	ADHD subtype Inattentive subtype: 31% Hyperactive-impulsive subtype: .35% Combined subtype: 68% Prior stimulant treatment: 23.3% History of depression: 14.9% Substance abuse disorder: 7.3% Anxiety disorder: 1.9%
Adler 2008 (Lisdexamfetamine) US	Outpatients age 18 to 55 years with a primary diagnosis of ADHD via DSM IV. All subjects were required to meet at least 6 of the 9 DSM-IV-TR subtype criteria and to have moderate to severe ADHD as rated by a clinician at baseline (score of $\geq$28). Other inclusion criteria included 12-lead electrocardiogram with QT/QTc-F interval < 450 ms for men and < 470 ms for women, resting heart rate 40 to 100 bpm, PR interval < 200 ms, and QRS interval < 110 ms.	Lisdexamfetamine: 30 mg/day; 50 mg/day (forced dose escalation 30 mg/day week 1, 50 mg/day weeks 2-4); 70 mg/day (forced dose escalation 30 mg/day week 1, 50 mg/day week 2; 70 mg/day weeks 3 and 4), or placebo. Duration: 4 weeks	NR	Mean age: 35.1 Male: 54% White: 82.5%	ADHD-RS mean total score at baseline: 40.5 CGI-S score at baseline, percentage in each group Moderate: 35% Marked: 50.75% Severe: 14% Extreme: 0.25%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Adler 2008 (Atomoxetine) US	410	Atomoxetine: 167 (62%) withdrawn; 48 (18%) lost to FU Placebo: 71 (51%) withdrawn; 16 (12%) lost to FU Number analyzed per drug: atomoxetine n=NR placebo n=NR	Atomoxetine vs. placebo EWPS (Work productivity) Mean reduction in impairment 16.2 points (atomoxetine) vs. 15.6 points (placebo) (NS) Quality of Life: mean change productivity 17.3 (Atomoxetine); 14.7 (placebo) (NS) relationships 12.2 (Atomoxetine); 11.8 (placebo) (NS) life outlook 10.4 (Atomoxetine); 6.8 (placebo) (P=.025) psych health 12.9 (Atomoxetine); 9.8 (placebo) (NS) DBS (Driving behavior) Self report total score NR observer ratings subsample: mean improvement (Atomoxetine) 6.1; (placebo) 2.0 (P=.011) ADHD Efficacy measures CAARS-S:SV (mean change -- baseline to endpoint (Atomoxetine) -11.5; (placebo) -9.9 (P=.027) Other efficacy measures (NS)
Adler 2008 (Lisdexamfetamine) US	420	71/2/414 lisdexamfetamine 30 mg: 115 lisdexamfetamine 50 mg: 117 lisdexamfetamine 70 mg: 120 placebo: 62	Change (LS mean) in ADHD-RS scores from baseline to endpoint: ITT population (N= 414) placebo: -8.2 (NS) lisdexamfetamine 30 mg: -16.2 (P<.0001) lisdexamfetamine 50 mg: -17.4 (P<.0001) lisdexamfetamine 70 mg: -18.6 (P<.0001) Post hoc analysis: > 30% reduction in ADHD-RS scores (% responding) -- data displayed on a graph, percentages are approximate. placebo: 35% lisdexamfetamine 30 mg: 60% lisdexamfetamine 50 mg: 68% lisdexamfetamine 70 mg: 70% CGI-I Score: % improved or very much improved: placebo: 29% lisdexamfetamine 30 mg: 57% lisdexamfetamine 50 mg: 62 % lisdexamfetamine 70 mg: 61%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Adler 2008 (Atomoxetine) US	Atomoxetine vs placebo Nausea 28.4%; 5.8% (P≤.001) Other adverse events that occurred in ≥ 5% sample and were statistically sig. Dry mouth, fatigue or insomnia, decreased appetite, constipation, erectile dysfunction, and urinary hesitation (individual rates were not reported)	Atomoxetine: 167 (62%); Placebo: 71 (51%) withdrawals due to AE 14% atomoxetine vs. 2.2% placebo (P≤ .001)	NR	Week 9: Participants not responding to treatment (no change or worsening of symptoms) using the CAARS-S:SV total score were discontinued from the study.
Adler 2008 (Lisdexamfetamine) US	Placebo vs Lisdexamfetamine 30mg/d vs Lisdexamfetamine 50mg/d vs Lisdexamfetamine 70mg/d Anorexia: 0 vs 4(3%) vs 8(7%) vs 6(5%) Anxiety: 0 vs 5(4%) vs 7(6%) vs 9(7%) Decreased appetite: 1(2%) vs 34(29%) vs 33(28%) vs 28(23%) Diarrhea: 0 vs 8(7%) vs 12(10%) vs 4(3%) Dry mouth: 2(3%), 25(21%) vs 29(25%) vs 38(31%) Feeling Jittery: 0 vs 2(2%) vs 4(#%) vs 9(7%) Insomnia: 3(5%) vs 23(19%) vs 20(17%) vs 26(21%) Nausea: 0 vs 10(8%) vs 7(6%) vs 8(7%)	Total withdrawals: 10 (16%) placebo 16 (13%) Lisdexamfetamine 30mg/d 21 (18%) Lisdexamfetamine 50mg/d 24 (20%) Lisdexamfetamine 70mg/d Due to AEs: 1 (2%) Placebo 4 (3%) Lisdexamfetamine 30mg/d 8 (7%) Lisdexamfetamine 50mg/d 9 (7%) Lisdexamfetamine 70mg/d	Shire Development Inc.	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Adler 2009 ("Atomoxetine treatment in adults…") US	Patients 18-65 years meeting DSM-IV-TR diagnoses for both ADHD and social anxiety disorder. Total LSAS score of at least 50 at visit 1, no more than a 30% decrease in LSAS total score at visit 2 and a CGI of O-S score of ≥4 at visits 1 and 2. Concomitant Axis I diagnoses (current or lifetime) specific phobias, GAD and dysthymia were allowed. Diagnosis of MDD was allowed only if diagnosis was >6 months before Visit 1.	A. Atomoxetine 40-100mg/d(mean final dose 82.9mg/d B. Placebo Treatment period: 2 wk placebo lead-in followed by 14 wk treatment	NR	Mean age: 38 years Male: 53.6% Ethnicity Caucasian: 74.0%	ADHD subtype Inattentive and hyperactive/impulsive symptoms:57.2% GSAD: 86.9% GAD: 23.3%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Adler 2009 ("Atomoxetine treatment in adults…") US	342	178/75/442	Atomoxetine vs placebo LOCF analysis Mean change from baseline in CAARS:Inv:SV Total ADHD symptom score:-8.7 vs -5.6 (95% CI -6.0 to -2.2), p<0.001. Results similar when all randomized patients were analyzed (p<0.001) Mean change from baseline in CAARS:Inv:SV ADHD index subscale -5.7 vs -3.2, p<0.001, similar results obtained from MMRM analysis p<0.001 and all randomized patients Mean change from baseline in CAARS:Inv:SV hyperactivity/Impulsivity subscale -3.9 vs -2.0, p<0.001, similar results obtained from MMRM analysis p<0.001 and all randomized patients Mean change from baseline in CAARS:Inv:SV Inattention subscale -4.8 vs -3.6, p=0.001 Mean Change from baseline in LSAS Total score: -22.9 vs -14.4 , p<0.001, similar results from MMRM analysis (p<0.001) and all randomized patients Pearson's correlation post-hoc analysis of CAARS:Inv:SV Total ADHD symptom scores and LSAS total scores mean change from baseline to LOCF endpoint: r=0.61; 95% CI 0.54 to 0.67 Mean change from baseline in CGI-O-S: -0.76 vs -0.60, (95% CI -0.39 to -0.33)p=0.02, MMRM analysis atomoxetine superior to placebo p=0.014 Mean change from baseline in AAQoL total score: 14.9 vs 11.1,(95% CI 0.35 to 7.0) p=0.03 Mean change from baseline in total ADHD symptom scores in patients without GAD: -8.40 vs -4.69, p<0.001 Mean change from baseline in total ADHD symptom scores in patients with GAD: -8.26 vs -5.52, p=0.295 Mean change from baseline in LSAS total scores in patients without GAD: -21.82 vs -12.16, p<0.001 Mean change from baseline in LSAS total scores in patients with GAD: -18.16 vs -13.39, p=0.556

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Adler 2009 ("Atomoxetine treatment in adults…") US	Atomoxetine vs placebo Insomnia: 17% vs 9%, p=0.010 Nausea: 16% vs 7.6% Dry mouth: 15.6% vs 4.3% Dizziness: 7.5% vs 2.4%, p=0.023 Mean change from baseline in weight: -0.41 to -0.08, p=0.190	Atomoxetine vs placebo Total withdrawals: 43.3% vs 37.2% Withdrawals due to AE: 10.3% vs 8.3%	Eli Lilly and company	Efficacy outcomes reported specifically from LOCF analysis although no. of patients included in LOCF not specified. It is reported that analysis of all randomized patients gave similar results.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Adler 2009 Companion to Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine)	Use of sleep-inducing medications was prohibited. However, diphenhydramine and diphenhydramine hydrochloride were used by 10 subjects (placebo: 2; 30 mg/d LDX: 6; 50 mg/d LDX: 1; 70 mg/d LDX: 1). Some instances of diphenhydramine use were related to treatment of allergic reactions/poison ivy or to respiratory symptoms and not for treatment of sleep disorders. Zolpidem tartrate and melatonin were each used by 1 subject during the study (30 mg/d LDX and placebo group, respectively).	See Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Adler 2009 Companion to Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine)	Placebo vs lisdexamfetamine 30mg/d vs lisdexamfetamine 50 mg/day vs lisdexamfetamine 70 mg/d vs lisdexamfetamine all doses PSQI: Change in Sleep Onset, LS mean (SE) in minutes: -1.2 (2.78) vs -3.5 (2.09) vs 0.4 (2.06) vs 4.0 (2.04) vs 0.4 (1.23) Change in Sleep Duration, LS mean (SE) in hours: -0.1 (0.15) vs -0.1 (0.11) vs -0.3 (0.11) vs -0.2 (0.11) vs -0.2 (0.07) Global score, LS mean (SE) change, placebo vs combined lisdexamfetamine groups: -0.5 (0.26) vs -0.8 (0.11); P= 033. Change in Daytime Dysfunction score, LS mean (SE), placebo vs combined lisdexamfetamine groups: 0.0 (0.08) vs -0.3 (P ≤0.01) vs -0.3 (P≤0.01) vs -0.4 (P≤0.01) vs -0.4 (0.04; P =0.0001) The mean changes from baseline at endpoint for the components of the PSQI, subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, and use of sleep medication, were not significantly different between patients treated with any lisdexamfetamine dose and those receiving placebo.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Adler 2009 Companion to Adler 2008 (Lisdexamfetamine)	Placebo vs lisdexamfetamine 30mg/d vs lisdexamfetamine 50 mg/day vs lisdexamfetamine 70 mg/d vs lisdexamfetamine all doses Sleep-related treatment-emergent AEs: Initial insomnia: 2 (3.2%) vs 4 (3.4%) vs 7 (6.0%) vs 7 (5.7%) vs 18 (5.0%) Insomnia: 3 (4.8%) vs 23 (19.3%) vs 20 (17.1%) vs 26 (21.3%) vs 69 (19.3%) Middle insomnia: 0 (0%) vs 5 (4.2%) vs 2 (1.7%) vs 6 (4.9%) vs 13 (3.6%) Somnolence: 2 (3.2%) vs 1 (0.8%) vs 0 (0%) vs 0 (0%) vs 1 (0.3%) Sleep disorder: 2 (3.2%) vs 0 (0%) vs 2 (1.7%) vs 0 (0%) vs 2 (0.6%) Abnormal dreams: 0 (0%) vs 0 (0%) vs 0 (0%) vs 1 (0.8%) vs 1 (0.3%) Early morning awakening: 0 (0%) vs 0 (0%) vs 0 (0%) vs 1 (0.8%) vs 1 (0.3%) Nightmare: 0 (0%) vs 0 (0%) vs 0 (0%) vs 2 (1.6%) vs 2 (0.6%) Poor quality sleep: 0 (0%) vs 1 (0.8%) vs 0 (0%) vs 0 (0%) vs 1 (0.3%) Hypersomnia: 0 (0%) vs 1 (0.8%) vs 0 (0%) vs 0 (0%) vs 1 (0.3%) Fatigue: 3 (4.8%) vs 9 (7.6%) vs 5 (4.3%) vs 3 (2.5%) vs 17 (4.7%)	See Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine)	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Adler 2009 US	Age 18-65 years with a minimum weight of 100 lbs (45.4 kg) at Screening. Diagnosis of ADHD as defined by the DSM-IV criteria with symptomatology from childhood to adulthood, symptoms present before age seven years and continue to meet full DSM-IV criteria at time of assessment. Diagnosis of ADHD confirmed by the Adult ADHD Clinical Diagnostic Scale (ACDS) at Baseline and Adult ADHD Investigator Symptom Rating Scale (AISRS) score of 24 or greater as determined by the Investigator at Baseline. Global Assessment of Functioning (GAF) Scale score of 41 to 60, inclusive, at Baseline.	MPH OROS Starting dose was 36 mg/d (subjects unable to tolerate the initial dose of 36 mg were discontinued from the study) Incremental dose increases of 18 mg every 7 days (±2 days) were continued until a protocol-defined response was achieved (36mg, 54mg, 72mg, 90mg, or 108mg) or the highest dose was reached (108 mg/d). Placebo All subjects assigned to placebo followed the same dosing schedule and procedures as those for the subjects randomized to MPH OROS. Duration: 7 weeks	No additional MPH or other ADHD medication	mean age: 39 years male: 56.8% Race: 86% Caucasian 6.1% African American 3.1% Asian 4.8% Other	ADHD subtype: combined 79.9% Baseline mean global assessment of functioning: MPH OROS 53.1; placebo 53

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Adler 2009 US	229	MPH OROS 42/8/110 (3 patients randomized failed to meet inclusion criteria and did not receive study packets) placebo 26/4/116	Primary Endpoint Least squares mean (LS Mean) change from baseline AISRS total score: MPH OROS (-10.6); placebo (-6.8), P=0.012. Secondary Endpoints Least squares mean final visit CGI-I score (lower values indicated improvement): MPH OROS (3.02); placebo (3.43) at the Final Visit (LOCF), p=0.008. Responders (subjects who had at least 30% improvement in the AISRS score and had a CGI-I score of 1 or 2 (very much improved or much improved). MPH OROS (36.9%) compared with the placebo group (20.9%) were responders at the Final Visit (LOCF), P=0.009.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Adler 2009 US	Total AE reported: MPH OROS 93 (84.5%); placebo 74 (63.8%) AE reported by at least 10% of MPH OROS subjects decreased appetite: MPH OROS 25.5%; placebo 6% headache: MPH OROS 25.5%; placebo 13.8% dry mouth: MPH OROS 20.0%; placebo 5.2% anxiety: MPH OROS 16.4%; placebo 3.4% nausea: MPH OROS 12.7%; placebo 2.6% blood pressure increased: MPH OROS 10%; placebo 5.2% Change in blood pressure and pulse Mean (SD) change in systolic blood pressure from baseline to the final visit was –1.2 (8.92) mm Hg for MPH OROS –0.5 (9.72) mm Hg for placebo. Mean (SD) change in diastolic blood pressure from baseline to the final visit was +1.1 (6.72) mm Hg for MPH OROS and +0.4 (7.43) mm Hg for placebo. Mean (SD) change in pulse was +3.6 (9.78) bpm for MPH OROS and –1.6 (8.33) bpm for placebo.	MPH OROS: 42 (due to AE n=16) placebo: 26 (due to AE n=6)	Johnson & Johnson Pharmaceutical Research and Development	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Barkley 2005 US	Not clear	Methylphenidate 10 mg, single dose (low dose) Methylphenidate 20 mg, single dose (high dose) Placebo Subjects were crossed over to each dose one time (i.e., all subjects took one dose of each of the three interventions), 75 minutes before testing began	allowed all other medications but stimulants	Mean age: 31.3 years (SD: 11.3) 74% male White: 83.3% African American: 3.7% Hispanic: 5.6% Native American: 5.6% Other: 1.9%	Combined subtype: 87% Predominantly Inattentive subtype: 11% Predominantly Hyperactive-Impulsive subtype: 0% ADHD not otherwise specified: 2% Never married: 67% Mean IQ: 104.7 (SD=9.7) Average number of years of driving experience: 14.5 years (SD: 11.1) Mean number of miles driven/week: 252 miles (SD: 203)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Barkley 2005 US	54	2 / 0 / 52 had complete data	Mean results for 1-baseline vs 2-MPH low vs 3-MPH high vs 4-placebo Standard course: Simulator self-rating: 55.7 vs 60.6 vs 61.9 vs 61.4 (p<0.001; pair-wise contrasts: 1<2,3,4) Simulator observer rating: 54.4 vs 60.1 vs 59.7 vs 59.2 (p<0.001; pair-wise contrasts: 1<2,3, 4) Number of crashes: 1.7 vs 0.9 vs 0.7 vs 0.9 (p<0.001; pair-wise contrasts: 1>2, 3, 4) Average speed and speed variability were not significantly different between groups; steering variability, course driving time, and number of turn signals given were significant between groups, but none showed a significant difference between MPH low and MPH high Only 44 of 54 patients could complete the obstacle course Conners Continuous performance test: Commission Errors: 13.3 vs 7.5 vs 7.2 vs 8.5 (p<0.001; pair-wise contrasts: 1>2, 3, 4; 4>3) Omission Errors: 4.2 vs 3.2 vs 2.0 vs 2.8 (not significantly different) Reaction time and reaction time variability did not differ significantly between the four groups

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Barkley 2005 US	The only AE reported was for simulator sickness.	Crossover design, thus withdrawals by treatment not given; unclear if patients who withdrew for part of a test completed the rest of the crossovers	National Institute of Child Health and Human Development, the Gerald J. and Dorothy R. Friedman Foundation for Medical Research, and the Frank and Nancy Parsons Foundation	All subjects were paid $150 at the end of the protocol.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Barkley 2007 US	Ages 21-65, composite IQ > 80, corrected or uncorrected visual acuity o no worse than 20/30, valid driver's license, no evidence of deafness, blindness, severe language delay, cerebral palsy, epilepsy, autism, or psychosis. DSM-IV ADHD diagnosis. DSM criteria met for both current functioning and using retrospective reports of childhood behavior between ages 5-7.	Placebo for 4 weeks w/ sham upward titration after 1 week Atomoxetine 0.6 mg/kg for 1 week and upward titration to 1.2 mg/kg daily for 3 weeks.	NR	Mean age 36.1 44% male ethnicity: 94% white 6% African American	ADHD subtypes: combined type: 72% inattentive type: 28% Mean education in years: 15.2 IQ (Shipley): 110.8
Biederman 2006	Outpatients 19–60 years. To be included, subjects had to satisfy full diagnostic criteria for DSM-IV ADHD on the basis of clinical assessment and confirmation by structured diagnostic interview	Osmotic release oral system methylphenidate (OROS MPH) vs. placebo titrated to optimal response (a maximum daily dose of 1.3 mg/kg; initial dose of 36 mg 6 weeks	No	Placebo/OROS MPH Age 37.6/32.7 Male 47%/57% Ethnicity NR	Placebo/OROS MPH CGI Severity Mild 0/1 Moderate 56/40 Marked 29/38 Severe 3/1 P = 0.1 Lifetime Psychiatric Comorbidity 46% / 33% P = 0.1

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Barkley 2007 US	20	4/ 0 Analyzed: rating scale: 18 subjects simulator data: 16 subjects	ADHD rating scale (placebo vs. atomoxetine) self -- symptoms: P=.011; Cohen's d: 0.94 self -- impairment: P=.005; Cohen's d: 0.94 other -- symptoms: NS other -- impairment: NS Side effects number (placebo vs. atomoxetine): P<.001; Cohen's d 1.62 Driving rating scales (difference from baseline): Driving Anger Scale -- self: NS Safe Driving Behavior -- self: P=.029; Cohen's d 0.72 Safe Driving Behavior -- other: NS Simulator ratings (placebo vs. atomoxetine): Driving behavior -- self: . P=.042 Cohen's d 0.39 Driving behavior / driving performance -- other: NS Simulator Scores (NS)
Biederman 2006	149	Placebo/MPH Withdrawn 11/18 Lost to F/U 4/7 Analyzed 74/67	Response of much or very much improved on the Clinical Global Impression–Improvement scale plus a >30% reduction in Adult ADHD Investigator System Report Scale score Placebo 39% vs. OROS MPH 66% P = NR

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Barkley 2007 US	Drug effects number: Difference from baseline Atomoxetine 2.5 vs. .1 placebo Individual adverse effects not reported	2 atomoxetine/ 2 placebo 0 withdrawals due to AE	NR	
Biederman 2006	OROS MPH / Placebo n(%) Decreased Appetite (Anorexia) 23 (34) / 2 (3) , P < .001 Dry Eyes, Nose, Mouth 23 (34) / 5 (7) P < .001 Headache 21 (31) / 22 (30) P = .8 Gastrointestinal 19 (28) / 10 (14) P = .03 Colds/Allergies/Infections 12 (18) / 18 (24) , P = .4 Tension/Jitteriness 12 (18) / 0 (0) , P < .001 Sleep Problems 12 (18) / 4 (5) , P = .02 Aches/Pains 9 (13) / 10 (14) , P = .9 Cardiovascular Complaints 6 (9) / 1 (1) , P = .04 Depression 5 (8) / 0 (0) , P = .02 Agitation 5 (7) / 6 (8) , P = .9 Dizziness 5 (7) / 0 (0) , P = .02 Menstrual Problems 2 (7) / 0 (0) , P = .1 Anxiety 4 (6) / 0 (0) , P = .03 Change in Systolic BP 3.5 vs. -1.1 P = 0.02 Diastolic BP 4.0 vs. -2.1 P < 0.001 Heart rate (bpm) 4.5 vs. -2.7 P < 0.001 QTC interval (msec) 1.9 vs. -1.2 P = 0.3	Placebo/MPH Total 11/18 Due to AEs (side effects) 3/9	McNeil Consumer and Specialty Pharmaceuticals	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Boonstra 2004 Netherlands (Cognitive outcomes from Kooij 2004)	see Kooij 2004	see Kooij 2004. For the 43 patients analyzed in this paper, the mean daily dose of MPH was 70.6 mg (SD: 16.7) Mean dose mg/kg/d was 0.93 mg/kg/d (SD: 0.18)	NR	(these are statistics for the 43 who completed the trial without protocol violations) Mean age: 38.9 years 48.8% male Ethnicity: NR	(these are statistics for the 43 who completed the trial) 95.3% had ADHD combined subtype 4.7% had ADHD hyperactive / impulsive subtype Average IQ: 100.3 (SD: 17.9) Sheehan Disability scale (min 0, max 30): 22.8 (SD: 3.3) Global Assessment of Functioning (min 0, max 100): 57.3 (SD: 6.1) Antisocial Personality Disorder: 9.3% Borderline Personality Disorder: 16.3%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Boonstra 2004 Netherlands (Cognitive outcomes from Kooij 2004)	45	2 / 0 / 43 43 subjects exposed to both treatments. This analysis excluded two patients who were included in the Kooij analysis.	Mean test results, MPH vs placebo: CPT: Mean hit reaction time: 342.6 vs 333.5, p=0.029 Standard error: 4.9 vs 6.0, p=0.11 Commission errors: 10.7 vs 13.6, p=0.002 Attentiveness: 3.4 vs 3.1, p=0.007 Risk taking: 0.7 vs 0.6, p=0.837 Change Task variables, over all 7 weeks: (univariate tests revealed significant interactions of treatment condition and treatment order for mean reaction time (p=0.001) and standard deviation of reaction times (p=0.000)) Stop signal reaction time: 202.3 vs 220.0, p=0.87 Change response mean reaction time: 457.1 vs 475.3, p=0.033 Change response standard deviation reaction time: 113.2 vs 117.0, p=0.615 data for the first point of measurement (after 3 weeks) for the variables showing the significant interactions between treatment order and treatment condition: Mean reaction time: 407.4 vs 434.1, p=0.346 Standard deviation reaction time: 78.2 vs 96.9, p=0.52

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Boonstra 2004 Netherlands (Cognitive outcomes from Kooij 2004)	see Kooij 2004	see Kooij 2004	Mental Health Institute GGZ Delfland, Health Insurance Company DSW, Nationaal Fonds Geestelijke Volksgezondheid (National Foundation for Mental Health), De Hersenstichting (Brain Foundation), and the Board of Scientific Activities of the Reinier de Graaf Hospital in Delft	This analysis did not analyze data from 2 non-compliant patients who were included in the original paper (see Kooij 2004).

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Boonstra 2007 Netherlands (Companion to Kooij 2004)	Adults (age not specified) with current diagnosis of ADHD and childhood diagnosis of ADHD using DSM-IV.	Placebo (dose not reported) and Methylphenidate (MPH) dosing was initiated at .5 mg/kg/d week 1, .75 mg/kg/d week 2, and up to 1 mg/kg/d in week 3. Medication was dosed 4 or 5 times daily. Last dose given at 20:00 (8:00 PM).	Not reported (NR)	Mean age 37.9 48% male 52% female ethnicity: NR	ADHD subtype 1 (3%) ADHD hyperactive / impulsive subtype 32 (97%) ADHD combined subtype None of the participants had been treated with MPH prior to the study.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Boonstra 2007 Netherlands (Companion to Kooij 2004)	33	2/0/# analyzed per drug NR	Sleeping problems reported in 33% MPH compared to 22% placebo Mean scores (arbitrary units unless otherwise noted) Well-rested: 2.84 placebo; 3.03 MPH (NS) Sleep onset latency (hours): 0:17 placebo; 0:24 MPH (NS) Difficulty initiating sleep: 2.15 placebo; 2.33 MPH (NS) Nocturnal awakenings: 0.99 placebo; 0.82 MPH (P<0.01) Sleep quality: 2.47 placebo; 2.67 MPH (NS) Rested at wake up: 3.01 placebo; 3.12 MPH (NS)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Boonstra 2007 Netherlands (Companion to Kooij 2004)	82% MPH compared to 69% for placebo. Individual adverse effects not reported. Sleeping problems were reported in 33% MPH compared to 22% placebo.	withdrawals due to AEs 0/33	Mental Health Institute GGZ Delfland, Health Insurance Company DSW, Nationaal Fonds Geestelijke Volksgezondheid (National Foundation for Mental Health), De Hersenstichting (Brain Foundation), and the Board of Scientific Activities of the Reinier de Graaf Hospital in Delft	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Bouffard 2003 Canada (Fair)	DSM-IV diagnosis of ADHD; 1.5 or more on at least 1 ADHD self-report questionnaire (either CAARS or AAPBS); IQ >=80 on abbreviated WAIS-R	Methylphenidate or placebo (sugar pill) 30 mg/day for 2 weeks (10 mg tid,) followed by 45 mg/day for 2 weeks (15 mg tid). Subjects were randomly assigned to start either methylphenidate or placebo.	NR	Mean age 34 80% male Ethnicity NR	Mean IQ 101
Carpentier 2005	positive diagnosis of ADHD w/ 6 criteria from DSM IV	Day 1–3 1 tablet t.i.d. 15 mg Day 4–7 2 tablets t.i.d. 30 mg Day 8–14 3 tablets t.i.d. 45 mg and two weeks placebo repeated (so 4 rounds) Duration 8 weeks	one patient on methadone	Mean age=31.9 88% male race nr	Type of substance abuse Alcohol 52.0% Drug 92%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Bouffard 2003 Canada (Fair)	38	8 (21%) withdrawn Loss to followup NR 30 (79%) analyzed, same subjects exposed to both treatments (phases were combined in analysis)	Mean change in condition from baseline, methylphenidate 30 mg/day vs methylphenidate 45 mg/day vs placebo (*p-values compare placebo with methylphenidate*): Adult behavior problems -1 vs -1 -0.7 (p<0.005) CAARS -0.8 vs -0.9 vs -0.5 (p<0.01) CPT% commission error -17.1 vs -19.4 vs -9.8 (p<0.001) CPT% omission error -3.3 vs -3.0 vs -0.5 (p<0.1) Stop-signal task vs -35.8 vs -47 vs -29.05 (ns) HAM-R -0.4 vs -0.5 vs -0.35 (p<0.05) BDI -5.5 vs -5.5 vs -4.4 (ns) SCL-90-R -9.8 vs -11 vs -7.45 (ns) Obsessive-compulsive scale -12 vs -13 vs -7.5 (p<0.05) Hostility scale -6.0 vs -6.8 vs -3.5 (ns)
Carpentier 2005	25	6/3/2019	Mean (SD) ADHD rating scale Placebo 31.8 (12.7) MPH 27.6 (15.3) (P = 0.352) Clinical Observation scale Placebo 17.8 (8.1) MPH 14.0 (9.2) (P = 0.211) Clinical Global Impression scale Placebo 8.3 (3.9) MPH 6.5 (4.3) (P = 0.184) Responders 30% reduction in in all 3 treatment scales Placebo 5 MPH 9

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Bouffard 2003 Canada (Fair)	Change from baseline in % of subjects reporting condition, methylphenidate 45 mg/day vs placebo: Mild appetite loss +23 vs +5% (ns) Mild trouble sleeping -2 vs -7% (ns) Moderate trouble sleeping -13 vs -9% (ns) Mild headache -4 vs +5% (ns)	Methylphenidate vs placebo, Total withdrawals unclear by treatment group; 4 enrolled withdrew on methylphenidate "because they were not blind" to treatment. Withdrawals due to AEs (n=1, (2.6%), treatment group unclear.	FRSQ grant	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).
Carpentier 2005	MPH showed significantly more side effects than placebo (F = 4.30, df = 1.87, P = 0.03).	Total withdrawals 6 1 withdrawal due to AEs on placebo	Novadic-Kentron Institute	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Chronis-Tuscano 2009 US	Mothers: Mothers with children (ages 6-12 yrs) were assessed using the CAARS-S:SV. T-scores and the ADHD Index had to fall a minimum of > 1.5 SD above the mean for the participant's age and gender to proceed to the diagnostic treatment. Met DSM-IV criteria (4 or 5 symptoms of ADHD currently present, with evidence that full ADHD criteria were met prior to age 12 years. And functional impairment in at least 1 setting with history of impairment in at least 2 settings during childhood. Children: ages 6-12 years who met DSM-IV criteria between age 6-12 with no prior diagnosis of pervasive developmental disorder or mental retardation.	Phase 1: MPH OROS and placebo titrated for 5 weeks to until the following criteria were met: 30% reduction in CAARS scores, CGSI-S scale indicated normal / not ill (score of 1) or borderline (score of 2), and medication was well tolerated. Maximum does 90 mg/day. Phase 2: placebo or MPH OROS at maximally effective dose (mean dose 83.7mg/day) x 2 weeks Outcome measure repeated again at end of phase 2	NR	Mothers: age: 39.8 White: 91.3% Asian: 4.3% Hispanic: 4.3% Children: male: 57%	Mothers: ADHD subtype: combined type: 56.5% inattentive type: 34.8% hyperactive/impulsive type 8.7% Children: inattentive ADHD subtype: 13% comorbid oppositional-defiant disorder 65% conduct disorder 13% received stable med. doses 61%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Chronis-Tuscano 2009 US	23	1/2/20 total 11 placebo; 9 MPH OROS	ADHD symptom scores: phase 2 -- week 7 CAARS self-report inattention: MPH OROS 57.78; placebo 65.55 (-7.77) Cohen d (effect size) .48 hyperactivity/impulsivity: MPH OROS 49.33; placebo 48.27 (-1.06) Cohen d (effect size) .06 ADHD index: MPH OROS 54.44; placebo 60.27 (-5.83) Cohen d (effect size) .38 CGI-S: MPH OROS 3.11; placebo 3.3 (-.19) Cohen d (effect size) .15 Parenting scores: APQ: phase 2 -- week 7 Involvement: MPH OROS 40.67; placebo 38.00 (-2.67) Cohen d (effect size) .52 Positive parenting: MPH OROS 24.22; placebo 24.82 (-.6) Cohen d (effect size) .15 Poor monitoring/ supervision: MPH OROS 11.44; placebo 13.27 (-1.83) Cohen d (effect size) .70 Inconsistent discipline: MPH OROS 12.00; placebo 14.63 (-2.63) Cohen d (effect size) .71 Corporal punishment: MPH OROS 3.33; placebo 3.64 (-.31) Cohen d (effect size) .42

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Chronis-Tuscano 2009 US	Reported for titration phase only: tics, buccal, picking skin, worried, dull/listless, headache, stomachache, irritable, tearful, withdrawn, hallucinations, appetite loss, sleep trouble heart rate, beats/min NS systolic blood pressure NS diastolic blood pressure NS weight/ kg baseline: 74.49 kg vs. 73.39 (54 mg), 73.08 (72 mg), 73.39 (90 mg) significant at $\leq$ .05.	3 during phase 1 (not randomized at that point) Withdrawals due to AE 1(MPH OROS)	McNeil Pediatrics	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Cox 2000 US (Fair)	ADHD and non-ADHD male subjects with no other current comorbidity were recruited from the local community from TV and computer bulletin board notices, as well as direct physician referrals. ADHD subjects were required to have previously taken Ritalin, but could not be taking any medication for their condition within the past 6 months. To confirm DSM-IV criteria for ADHD, participants were interviewed using Barkley's structured interview for ADHD and the DSM-III-R criteria. ADHD subjects had current and childhood symptoms, consistent with DSM-III-R criteria.	Methylphenidate 10 mg/day, single dose Placebo (vitamin C), single dose Subjects were admitted to the research center to control for diet and sleep conditions. On the following day at 8AM, subjects received either placebo or methylphenidate at 8AM. 1.5 hours after taking the medication, subjects drove for 30 minutes on a simulator. At 3:30PM, subjects received the alternative treatment (placebo or methylphenidate) than that received at 8AM. 1.5 hours after taking the medication, subjects drove for 30 minutes on a simulator using an alternative driving scenario.	NR	Mean age 22.0 100% male 77% white 15% black 7.7% Asian	ADHD patients vs non-ADHD controls: Mean # motor vehicle violations, 2.6 vs 1.5 (p=0.06) Mean # automobile crashes, 2.7 vs 0.8 (p=0.018)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Cox 2000 US (Fair)	13	0% withdrawn; 0% loss to followup; 13 (100%) analyzed, same subjects exposed to both treatments (phases were combined in analysis)	Placebo vs Ritalin, mean Impaired Driving Score (score of 0 would be average, +1 would be one standard deviation worse than the mean): ADHD patients +0.5 vs +2.4 (p=0.05) Non-ADHD controls +0.6 vs -1.0 Mean self-rated driving performance, ADHD patients vs non-ADHD controls: Placebo: 3.0 vs 3.9 (p=0.05) Ritalin: 3.5 (+0.5 better than placebo) vs 3.6 (-0.3 worse than placebo), (ns)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Cox 2000 US (Fair)	NR	Methylphenidate vs placebo, Total withdrawals: 0 vs 0 Withdrawals due to AEs: 0 vs 0	University of Virginia Health Sciences Center grant	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 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Goodman 2005 QU.E.S.T.	outpatients >18 years of age who were referred by clinics and had a primary diagnosis of ADHD established by psychiatric evaluation using *DSM-IV-TR* criteria	Daily morning dose of placebo MAS XR 20 mg, 40 mg, or 60 mg for 4 weeks	NR	Mean age (yrs): Placebo 39.3 20mg 38.8 40mg 38.9 60mg 39.9 Male (%) Placebo 68 20mg 64 40mg 59 60mg 48 Ethnicity (%) White: Placebo 90 20mg 87 40mg 91 60mg 88 African American: Placebo 5 20mg 5 40mg 3 60mg 0 Hispanic: Placebo 3 20mg 6 40mg 3 60mg 8 Other: Placebo 2 20mg 2 40mg 3 60mg 3	Years since diagnosis Placebo 5.0 20mg 4.6 40mg 4.9 60mg 7.1 ADHD-RS (baseline) Placebo 33.0 20mg 31.1 40mg 31.3 60mg 32.9

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Goodman 2005 QU.E.S.T.	255	Number withdrawn Placebo 22 20mg 19 40mg 15 60mg 16 Lost to FU Placebo 2 20mg 4 40mg 1 60mg 3 Analyzed Placebo 60 20mg 64 40mg 64 60mg 60	SF-36 (version 2) Change from baseline to endpoint N=702 Changes are presented in table format and are estimated here for the purpose of reporting results physical functioning: change approximately. 5 points; P< .001 role/physical: change approximately. 9 points; P< .001 bodily pain NS general health: change approximately. 5 points; P< .001 vitality: change approximately. 20 points; P<.001 social functioning: change approximately. 10 points; P< .001 role/ emotional: change approximately. 20 points; P< .001 mental health: change approximately. 12 points; P< .001

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Goodman 2005 QU.E.S.T.	Placebo/20mg/40mg/60mg (%) Anorexia: 3/20/42/38 Insomnia: 13/21/30/26 Headache: 16% vs 4% (p=0.18)3/14/30/26 Nervousness: 13/11/16/12 Dry mouth: 5/24/44/38 Weight loss: 0/5/16/12 Nausea: 5/8/6/10 Agitation: 5/8/6/10 Anxiety: 3/6/6/10	Total withdrawals Placebo 22 20mg 19 40mg 15 60mg 16 Withdrawals due to AEs (%) Placebo 1 20mg 9 40mg 6 60mg 8	NR	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Gualtieri 1985 US (Fair)	Eight male subjects who met the diagnostic criteria for ADD-RT. Subjects had clinical histories consistent with ADHD during their primary school years, which were confirmed by parents and by review of medical or school records. All subjects continued to have difficulty with poor attention span and distractibility, restlessness and fidgety behavior, impulsiveness, emotional lability (especially temper outbursts), unsatisfactory level of efficiency at work, and difficult interpersonal relationships.	MPH (0.3 mg/kg) or Placebo were given on a bid schedule (8AM and 12 noon) for 5 days (Monday through Friday). On the second Monday, following a 68-hr washout period, the procedure was repeated with the alternative treatment.	NR	Mean age 27.2 100% male Ethnicity NR (represents n=22, of which 8 were included in the placebo-RCT)	In the total sample (n=22, of which 8 participated in the DB RCT), previous diagnoses included depressive neurosis (n=3), personality disorder (n=3), and alcoholism (n=1). Two subjects had narcolepsy.
Kay 2009 US (See note in comments section)	Age 19-25 with the following criteria satisfied. DSM-IV diagnosis of ADHD Score of $\geq$ 24 (severity worse to moderate range) on ADHD-RS rating scale Normal intellectual functioning (score $\geq$ 89 on Wechsler abbreviated Scale of Intelligence) Demonstrated no greater than average performance on at least two standardized measures of executive function (Stroop Color and Word Test; Halstead-Reitan Category Test)	Atomoxetine: titrated up to 80 mg/day x 3 weeks Placebo titrated up to 80 mg/ day x 3 weeks	NS	Mean age: 22.4 Male: 87.5% Caucasian: 56.3% African American: 18.8% Hispanic: 12.5% Asian 12.5%	Mean Weight (lbs): 178.3 Mean Height (inches): 70.3

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Gualtieri 1985 US (Fair)	8	NR/NR/8 N per drug not reported (phases were combined in analysis).	Placebo vs MPH: AAS: 27.7 vs 25.8, NS ZSDS: 45.3 vs 37.5, NS ZSAS: 38.3 vs 33.8, NS CPT correct: 121.8 vs 128.5, p <0.05 CPT errors: 5.3 vs 2.1, NS Actometer: 98.6 vs 60.3, NS Growth hormone: 1.3 vs 6.0, NS MPH significantly improved correct responses on the CPT. All subjects accurately guessed the active drug condition.
Kay 2009 US (See note in comments section)	16	2/0/8 each drug	**Mean Driving Scores (driving safety score = z score)** 2 hr. test: Placebo 0.021; Atomoxetine -0.024 P=NS 7 hr. test: Placebo 0.066; Atomoxetine -0.075 P=NS 12 hr. test: Placebo 0.037; Atomoxetine -0.032 P=NS Mean total score: placebo 0.018; Atomoxetine -0.021 P=NS <u>ADHD-RS and CGI-I scores:</u> ADHD-RS score: Improved from baseline: placebo 25%; Atomoxetine 40% (P=NS) CGI-I: subjects rated as very much/ much improved: placebo 6.3%; Atomoxetine 13.3% (P=NS)

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Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Gualtieri 1985 US (Fair)	AEs were not reported among the 8 subjects who participated in the short-term DB RCT.	Methylphenidate vs placebo, Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0	USPHS Grant HD-10570	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.
Kay 2009 US (See note in comments section)	Total AE reported: Atomoxetine (68%); placebo (56.3%) gastrointestinal: 43.8; 12.5% abdominal pain: 18.8%; 0 dry mouth: 12.5; 6.3% nausea: 18.8%; 6.3% general: 18.8; 12.5% weight decrease: 6.3%; 0 metabolism/ nutrition: 18.8%; 0 anorexia: 12.5%; 0 nervous system: 25; 12.5% headache:12.5; 12.5% somnolence: 12.5%; 0 Psychiatric: 12.5%; 0 Anger: 0; 6.3% Anxiety: 6.3%; 0 Insomnia: 0; 6.3% Irritability: 0; 6.3%	Atomoxetine 1; Placebo 0 Withdrawals due to AE 1 (atomoxetine); 0 (placebo).	Shire Pharmaceuticals	This study included two separate placebo controlled studies within a crossover study. Cohort 1: MAS XR vs. placebo Cohort 2: Atomoxetine vs. placebo

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Kay 2009 US (See note in comments section)	Age 19-25 with the following criteria satisfied. DSM-IV diagnosis of ADHD Score of ≥ 24 (severity worse to moderate range) on ADHD-RS rating scale Normal intellectual functioning (score ≥ 89 on Wechsler abbreviated Scale of Intelligence) Demonstrated no greater than average performance on at least two standardized measures of executive function (Stroop Color and Word Test; Halstead-Reitan Category Test).	Mixed amphetamine salts extended release (MAS XR) titrated up to 50 mg/day x 3 weeks Placebo titrated up to 50 mg/ day x 3 weeks	NS	Mean age: 22.3 Male: 89.5% Caucasian: 78.9% African American: 10.5% Asian 5.3%	Mean Weight (lbs): 173.8 Mean Height (inches): 69.2
Kinsbourne 2001 US (Fair)	Subjects were selected from consecutive adult clinic referrals based on the following: 1) history of symptoms meeting DSM-IV ADHD (at least 6 of 9 inattentive and/or hyperactive/impulsive symptoms); 2) full DSM-IV criteria for ADHD met in childhood, in retrospect; 3) have no other psychiatric disorder that would explain their symptoms of ADHD; 4) gave informed consent.	Methylphenidate 5, 10, and 20 mg/day Placebo Each dose of MPH or placebo was administered in a single dose, in a randomized sequence, in the morning on each of four days. Duration 4 days	NR	Mean age 34 41.2% male Ethnicity NR	None of the subjects had been previously diagnosed with ADHD, and none were currently taking psychoactive drugs.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Kay 2009 US (See note in comments section)	19	4/0/MAS XR 8/placebo 7	Mean Driving Scores (driving safety score = z score) 2 hr. test: Placebo 0.28; MAS XR -0.26 (0.54) P=NS 7 hr. test: Placebo 0.33; MAS XR -0.31 (0.64) P=0.013 12 hr. test: Placebo 0.31; MAS XR -0.29 (6) P=0.005 Mean total score: placebo 0.3; MAS XR -0.29 P=0.014 ADHD-RS and CGI-I scores: ADHD-RS score: Improved >30% baseline: MAS XR 80%; placebo 13.3% P=0.0004 CGI-I: subjects rated as very much/ much improved: MAS XR 66.7%; placebo 0% P=NE
Kinsbourne 2001 US (Fair)	17	0% withdrawn 0% lost to followup 17 (100%) analyzed; N per drug not reported (phases were combined in analysis)	12% were non-responders; their best performance was on placebo. 88% were favorable responders; 41% performed optimally at 5 mg; 12% at 10 mg; 35% at 20 mg

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kay 2009 US (See note in comments section)	Total AE reported: MAS XR 12 (75%); placebo 3 (16.7%) gastrointestinal: MAS XR 3 (18.8%); 1 (5.6%) dry mouth: MAS XR 3 (18.8%); placebo 0 nausea: MAS XR 1 (6.3%); placebo 1 (5.6%) general: MAS XR 1 (6.3%); placebo 1 (5.6%) weight decrease: MAS XR 4 (25%); placebo 1 (5.6%) metabolism/ nutrition: MAS XR 8 (50%); placebo 0 anorexia: MAS XR 8 (50%); placebo 0 nervous system: MAS XR 4 (25%); placebo 1 (5.6%) headache: MAS XR 2 (12.5%); placebo 1 (5.6%) Psychiatric: MAS XR 7 (43.8%); placebo 0 Anger: MAS XR 2 (12.5%); placebo 0 Anxiety: MAS XR 2 (12.5%); placebo 0 Bruxism: MAS XR 3 (18.8%); placebo 0 Insomnia: MAS XR 3 (18.8%); placebo 0 Irritability: MAS XR 2 (12.5%); placebo 0	MAS XR 1; Placebo 3 Withdrawals due to AE 1 (MAS XR); 1 (placebo).	Shire Pharmaceuticals	This study included two separate placebo controlled studies within a crossover study. Cohort 1: MAS XR vs. placebo Cohort 2: Atomoxetine vs. placebo (see Atomoxetine section)
Kinsbourne 2001 US (Fair)	NR	Methylphenidate (5/10/20 mg/day) vs placebo, Total withdrawals: 0/0/0 vs 0. Withdrawals due to AEs: 0/0/0 vs 0	NR	Data from the first treatment phase was not reported separately.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Kollins 2011 Companion to Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine) This post-hoc analysis was conducted using data from a subset of the original population: 36 participants with a history of depression (compared to 378 participants without a history of depression); and 17 participants with a history of SUD (all by chance randomized to LDX, compared with 397 participants without a history of SUD)	See Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Kollins 2011 Companion to Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine)	See Adler 2008 (Lisdexamfetamine)	Mean change in ADHD-RS-IV scores from baseline to endpoint: Participants taking LDX in the overall study vs with a history of depression vs without a history of depression: -17.5 (SD 12.07) vs -14.9 (SD 11.38; effect size d=0.58; 95% CI, CI -0.37 to 1.53) vs -17.8 (SD 12.12; effect size d=0.86; 95% CI, CI 0.57 to 1.14) Participants taking placebo in the overall study vs with a history of depression vs without a history of depression: -7.8 (SD 9.28) vs -8.2 (SD 12.91) vs -7.8 (SD 9.05) Participants with vs without a history of SUD: Receiving LDX: -16.7 (SD 10.25) vs -17.6 (SD 12.16) Receiving placebo: NA vs -7.8 (SD 9.28); no patients taking placebo had a history of SUD Percentage of participants who were categorized as improved on the CGI-I at study endpoint, overall study vs with a history of depression vs without a history of depression: Receiving LDX: 60% vs 52% vs 60% Receiving placebo: 29% vs 20% vs 30% Percentage of participants who were categorized as improved on the CGI-I at study endpoint, with vs without a history of SUD: Receiving LDX: 65% vs 59% Receiving placebo: NA vs 29%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kollins 2011 Companion to Adler 2008 (Lisdexamfetamine)	Participants with vs without a history of depression: Any treatment-emergent AE: 78.1% vs 78.8% Psychiatric treatment-emergent AEs: 37.5% vs 37.1% Decreased appetite: 25.0% vs 26.7% Insomnia: 18.8% vs 19.3% Headache: 15.6% vs 21.2% Treatment-emergent AEs with incidence of ≥5% and a ≥50% difference between participants with and without a history of depression: Anxiety: 9.4% vs 5.5%) Diarrhea: 3.1% vs 7.1% Dry mouth: 37.5% vs 24.5%) Irritability: 0% vs 6.1% Upper respiratory tract infection: 0% vs 5.8% Participants with vs without a history of SUD: Any treatment-emergent AE: 83.3% vs 78.5% Decreased appetite: 22.2% vs 26.8% Dry mouth: 33.3% vs 25.3% Insomnia: 22.2% vs 19.1% Treatment-emergent AEs with incidence of ≥5% and a ≥50% difference between participants with and without a history of SUD: Anorexia: 11.1% vs 4.5% Anxiety: 16.7% vs 5.0% Diarrhea: 0% vs 6.7% Headache: 44.4% vs 18.4% Initial insomnia: 0% vs 5.0% Nausea: 11.1% vs 6.4% Upper respiratory tract infection: 0% vs 5.6% Note: Only AEs reported in the LDX group were reported in this article; see main publication for more AE information	Participants taking LDX with vs without a history of depression: Total withdrawals: 15.6% vs 17.2%; similar to overall study population Due to treatment-emergent AEs: 4 (11.1%) vs 18 (4.8%) Participants taking LDX with vs without a history of SUD: Total withdrawals: 16.7% vs 17.1%; similar to overall study population Due to treatment-emergent AEs: 2 (11.8%) vs 19 (4.9%)	Shire Development Inc.	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Konstenius 2010 Sweden	Amphetamine dependent patients 18-65 years old newly diagnosed with ADHD, who fulfilled the DSM-IV criteria for amphetamine dependence during the previous 12-month period.	A: Extended-release (OROS) methylphenidate 18-72 mg B: Placebo for 13 weeks Study drug was titrated over a period of 10 days; for subjects who did not tolerate a dose increase, the dosage was adjusted and continued at the tolerated level.	NR Drug use during the study (pos u-tox, mean): Amphetamines: 9.6 (SD 8.6) Other illicit drugs: 3.8 (SD 3.7)	Mean age: 37.4 years (SD 9.9) Male: 75% Ethnicity NR	Mean chronic amphetamine use: 13.9 years Mean debut in drug use: 14.1 years Age of onset of amphetamine use: 18.4 years Age of onset any drug use: 13.9 years Self-reported abstinence of amphetamine use before study inclusion: 3.5 months Lived on social welfare: 71%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Konstenius 2010 Sweden	24	NR/NR/24	Placebo vs Methylphenidate Drug use during the study (pos u-tox) (mean, SD): Amphetamines: 8.6 (7.8) vs 10.6 (8.8); P=0.472 Other illicit drugs: 3.5 (3.7) vs 4.1 (3.6); P=0.501 Days of drug use during study (self-reported) (mean, SD): Amphetamines: 4.1 (4.9) vs 4.6 (7.9); P=0.698 Other drugs: 4.6 (7.0) vs 0.5 (1.0); P=0.160 Alcohol < 60 g/day: 12.3 (16.4) vs 1.3 (2.0); P=0.038 Alcohol > 60 g/day: 8.0 (9.8) vs 4.2 (10.0); P=0.184 Retention in treatment completers: 84% vs 59%; P=0.187 Longest period of abstinence (weeks, mean, SD): 3.9 (3.0) vs 4.6 (3.4); P=0.614 Time to relapse (urine sample, mean): 3.8 (95% CI, 2.2 to 5.4) vs 3.333 (95% CI, 1.8 to 4.9) Change from baseline to LOCF: ADHD symptoms (mean, SD) CAARS:SV: -8.5 (19.8) vs -19.1 (13.2); P=0.137 CAARS:O: -4.0 (13.8) vs-3.9 (11.9); P=0.686 Other measures (mean, SD): Craving: 2.8 (1.8) vs 2.3 (1.3); P=0.670 BDI: (0.4 (6.0) vs -6.9 (9.8); P=0.138 BAI: (3.4 (4.1) vs -0.5 (6.4); P=0.098 Stroop: -2.6 (22.0) vs -7.0 (9.4); P=0.193

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Konstenius 2010 Sweden	Reported adverse events were mild and reversible and abided over time. Most common were headache and nausea. One participant required reduced dosage due to nervousness. Only one severe AE was reported, blurred vision, which temporarily occurred in one participant. This was reversible and disappeared with dose reduction.	NR	Study medication donated by Jansen Cilag, Sweden	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Kooij 2004 Netherlands	Outpatient adults with ADHD aged 20 to 56 years, with current ADHD (at least 5 of 9 symptoms of inattention and/or hyperactivity /impulsivity) and childhood onset with at least 6 of 9 symptoms in one or both symptom domains.	Methylphenidate and placebo. MPH was started at 0.5 mg/kg/day by week 1, increased to 0.75 mg/kg/d by week 2, and was up-titrated to 1.0 mg/kg/d by week 3 unless adverse events emerged. Treatment was 3 weeks long. There were two 3-week treatment periods with 1 week of washout in-between the crossover.	NR	Mean age: 39.1 years 53.3% male Ethnicity: NR	95.5% had ADHD combined subtype 4.5% had ADHD hyperactive / impulsive subtype Average IQ: 101 (SD: 18) School failure: 76% Sheehan Disability scale (min 0, max 30): 22.8 (SD: 3.3) Global Assessment of Functioning (min 0, max 100): 57.3 (SD: 6.1) Co-morbid Antisocial or Borderline Personality Disorder: 33% Baseline HAMD: 8.0 (SD: 5.8) Baseline HAMA: 7.8 (SD: 6.0) Any substance use disorder: 51%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Kooij 2004 Netherlands	45	0 / 0 / 45 same subjects exposed to both treatments	% of responders at end of treatment periods, methylphenidate vs placebo: DSM-IV ADHD rating scale combined with CGI-S: 38% vs 7%, p=0.003 DSM-IV ADHD rating scale only: 42% vs 13%, p=0.011 CGI-S scale only: 51% vs 18%, p=0.011 Compliance data (taking medicine >80% of time; for 41 patients): 68.3% compliant 31.7% non-compliant Mean decrease in scores for methylphenidate vs placebo, p-value: DSM-IV ADHD: -0.19, p=0.064 CGI-S: -0.72, p=0.026 SDS: -0.93, p=0.029 GAF score: +2.5, p=0.104 HAMD: +2.4, p=0.002 (i.e., MPH is associated with higher symptom leves of depression) HAMA: +2.9, p=0.002 (i.e., MPH is associated with higher symptom leves of anxiety)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kooij 2004 Netherlands	Methylphenidate vs placebo: % of patients on treatment reporting any AEs: 82% vs 69% (p=0.11) Loss of appetite: 22% vs 4 % (p=0.039) Sleeping problems: 33% vs 22% (p=0.27) Headache: 16% vs 4% (p=0.18) Tachycardia: 9% vs 2% (p=0.25) Dizziness: 16% vs 7% (p=0.34) Abdominal complaints: 13% vs 4% (p=0.22) Dry mouth: 24% vs 7% (p=0.06) Tics: 7% vs 2% (p=0.5) 18% of patients lowered their MPH dose due to AEs; none dropped out due to AEs Systolic blood pressure: +0.13 mmHg after MPH (p=0.954) compared to placebo Diastolic pressure "virtually unchanged" Mean heart rate: +4.8 beats/min higher after MPH (p=0.002) compared to placebo Mean body weight: -1.7kg after MPH (p<0.001) compared to placebo	0 / 0	Mental Health Institute GGZ Delfland, Delft; Parnassia, Psycho-Medical Centre, The Hague; Health Care Insurance Company DSW, Schiedam; Nationaal Fonds Geestelijke Volksgezondheid and De Hersenstichting, The Netherlands; Board of Scientific Activities of the Reinier de Graaf Hospital in Delft	Exclusion criteria included: clinically unstable psychiatric conditions, current use of psychotropics, prior use of methylphenidate or amphetamines, and a history of tic disorders.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Levin 2002 US (Fair)	Adults ages 19-56; all were positive for ADHD according to DSM-IV; all were nonsmokers verified by end tidal carbon monoxide measurements less than 8 ppm; an experienced clinical psychologist made the diagnoses of ADHD using the Wender Utah Rating Scale, the Conners/Wells Adolescent and Adult Self-Report, a modified version of Barkley's adult ADHD semistructured interview	Placebo Nicotine transdermal patches: Week 1=5 mg per day, Weeks 2-3=10 mg per day, Week 4: 5 mg per day Methylphenidate sustained release 20 mg per day Nicotine+methylphenidate sustained release Duration: 4 weeks	NR	Mean age=37 62.5% male race nr	NR

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Levin 2002 US (Fair)	40	6 (15%) withdrawn/lost to FU nr/34 analyzed (placebo n=7, nicotine n=9, MPH n=9, combination n=9)	MPH vs placebo (differences are NS unless otherwise noted) CGI Day 1 (acute): 5.0 vs 4.8 Days 15 and 28 (chronic): 5.4 vs 4.1 Change from baseline to day 28: -0.5 vs -0.6 POMS MPH vs placebo on day 21: F(1,26)=6.55, p=0.025; NS on days 1, 15 and withdrawal days (data nr) CPT Omission-- Acute: 2.4 vs 1.0; Chronic: 1.0 vs 1.3 Commission errors-- Acute: 16.6 vs 13.0; Chronic: 12.2 vs 13.1 Reaction time (ms)-- Acute: 324 vs 355; Chronic: 326 vs 329 Reaction time variability-- Acute: 7.8 vs 7.7; Chronic: 6.0 vs 6.0 Attention-- Acute: 2.7 vs 3.4; Chronic: 3.5 vs 3.0 ANAM Reaction time (ms): 280 vs 293 Spatial rotation (ms): 2,208 vs 2,198 Delayed matching (%): 91.9 vs 91.2

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Levin 2002 US (Fair)	NR	Methylphenidate vs placebo, Total withdrawals: 1 (10%) vs 3 (30%); p=NS Withdrawals due to adverse events nr	NR	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Levin 2006 US	Ages 18-60, meet DSM-IV criteria for opiate dependence and adult ADHD, on the same dose of methadone for at least 3 weeks	Placebo, sustained-release MPH, and sustained-release bupropion (BPR) 2-week placebo lead-in, 2-week dose titration period followed by 8 weeks at stable dose MPH titration phase standard formulation 2X/day starting at 10 mg/day increased by 10 mg/day, up to 40 mg/day, then standard formulation replaced by sustained-release formulation as two 20 mg doses, dose increased up to maximum of 80 mg/day. Patients discontinued if could not tolerate at least 40 mg/day MPH. BPR was started at 100 mg/day and increased by 100 mg by the end of the first week of the titration phase. Patients received 200 mg 2 X/day for the maximum dose of 400 mg/day by the end of the second week. Patients discontinued if could not tolerate at least 200 mg/day BPR.	Medication and treatment at a methadone program, weekly individual cognitive behavioral therapy for drug use	Mean age placebo/MPH/BPR 39/40/38, p=0.59 57% male 40% white 40% Hispanic 20% black	Currently employed at baseline placebo/MPH/BPR 43%, 58%, 89%, p=0.001 34% enrolled in methadone maintenance program for less than 12 weeks, 58% enrolled for more than 6 months

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Levin 2006 US	115	Placebo/MPH/BPR Withdrawn 8/11/10 Lost to F/U NR Analyzed 25/21/23	AARS response >30% reduction placebo 46%, MPH 34%, BPR 49%, p=0.48 CGI response improvement rating <3 placebo 39%, PMH 19%, BPR 30%, p=0.19 No significant differences in any drug or cocaine use.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Levin 2006 US	Fatigue 9% placebo Increased sweating MPH 6%, BPR 9% Nosebleed placebo n=1 Psychomotor agitation MPH n=1	Placebo/MPH/BPR Total withdrawn 8/11/10 Withdrawn AEs (side effects) 2/1/0	NIDA grants #R01 DA00144, K02 00465 and K02 DA 00288	

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Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Levin 2007 US	ages of 18–60 to meet DSM-IV criteria for cocaine dependence and persistent adult attention deficit hyperactivity disorder	Placebo and MPH dosing was initiated at 10 mg/day of standard formulation methylphenidate and increased up to 20 mg two times a day (40 mg/day) one week lead-in, two week titration and 11 weeks at stable dose	Not reported (NR)	Mean age 37.0 83% male 60% white 20% black 14% Hispanic 6% other	Employed full-time 72% placebo 50% MPH Baseline AARS Placebo 33.47 MPH 30.40
Marchant 2011 US	Adults between 18-65 years meeting DSM-IV Text-Revision criteria for ADHD and/or Utah criteria for ADHD and experiencing at least moderate impairment (a score of 4 or greater on the CGI-Severity Scale for ADHD at both screening and baseline visits.	A. Methylphenidate transdermal mean dose 23.8 (SD 6.6), range 10-30mg B. Placebo Crossover trial, 4 weeks each	NR	Age: 35.2 years Male: 73.5% Ethnicity: NR	Self report WRAADDS total score: 20.9

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Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Levin 2007 US	124	Placebo/MPH Withdrawn 29/30 Lost to F/U NR	AARS response rate 30% reduction Placebo 55% MPH 47% P = 0.44 Clinical Global Improvement scale (CGI) Placebo 30% MPH 34% P = 0.68 Targeted Adult Attention Deficit Disorder Scale (TAADDS) response 30% reduction Placebo 40% MPH 28% P = 0.22 No significant differences in cocaine use
Marchant 2011 US	67	15/NR/NR	Methylphenidate transdermal vs placebo (p-value vs placebo) Proportion of patients with change(improvement) in total WRAADDS With ADHD alone: -38% vs -8%, p=0.014 With ADHD+ODD: -72% vs -8%, p=0.024 Proportion of patients with change (improvement) in total CAARS With ADHD alone: -41% vs 3%(decline), p=0.031 With ADHD+ODD: -66% vs -21%, p=0.057

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Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Levin 2007 US	Headache placebo 2% MPH 8% GI upset placebo 4% MPH 8% Diarrhea placebo 9% MPH 2% Insomnia placebo 2% MPH 9%	Placebo/MPH Total 29/30 Due to AEs (side effects) 1/1 Most withdrew because "Not interested" 22/19	NIDA grants # ROI DA11755 and K02 00465	
Marchant 2011 US	Methylphenidate transdermal vs placebo (p-values are vs placebo) Proportion of patients with 1 AE: 30% vs 22% Sleep/Insomnia: 31% vs 7%, p=0.003 Headache: 13% vs 7%, p=0.039 Anxiety: 11% vs 2%, p=0.031 Decreased appetite: 11% vs 3%, p=0.180 Anger/Irritability: 11% vs 5%, p=0.344 Nausea: 7% vs 0%, p=0.125 Change from baseline in mean weight: -3.0 vs +0.8, p<0.001 Change from baseline in SBP: -2.7 vs -0.8, p=0.16 Change from baseline in DBP: -0.1 vs -0.4, p=0.36	Total withdrawals: NR by group Withdrawals due to AE: NR by group	Partly by Shire	Baseline characteristics reported on 90 patients, by subgroups: ADHD alone, ADHD+ED, ADHD+ODD, ADHD+ED+ODD

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Mattes 1984 US (Fair)	Subjects were drawn from a psychiatric outpatient clinic and via newspaper ads and given a questionnaire of 5 ADD symptoms (restlessness, difficulty concentrating, excitability, impulsivity, irritability). Subjects were aged 18-45, who met questionnaire criteria and received a psychiatrist rating of at least 2 on at least 3 of the 5 adult ADD symptoms. Subjects with history of childhood ADHD were assigned to experimental group; subjects with no childhood history were assigned to control group.	Methylphenidate or placebo: dosage began at 5 mg bid (8AM and 12 noon), increased to 10 mg bid every 2 days, to a maximum of 30 mg bid. Methylphenidate mean dose: 48.2 mg/day Placebo mean dose: 57 mg/day Sequence of drug phases was randomized. Each phase lasted three weeks, with no intervening washout period.	NR; drug or alcohol abuse was allowed	NR NR NR	29 patients with childhood ADHD 37 patients without childhood ADHD DSM-III diagnoses of subjects: ADD residual type 42.4% Antisocial personality disorder 7.6% Alcoholism 10.6% Drug abuse 24.2% Borderline personality disorder 24.2% Major depressive episode (mild) 28.8% Generalized anxiety disorder 10.6% Other 68.2%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Mattes 1984 US (Fair)	66	5 (7.6%) withdrawn; Loss to followup NR; 61(92.4%) analyzed; N per drug not reported (phases were combined in analysis).	No response to methylphenidate occurred in either patients with or without childhood ADHD. Results among patients without childhood ADHD were 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)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Mattes 1984 US (Fair)	The following AEs occurred significantly (p<0.05) with methylphenidate: more anorexia, headaches, late-afternoon depression, and less psychiatrist-rated impulsivity. Numeric results for AEs were not shown.	Methylphenidate vs placebo: Total withdrawals unclear by treatment group; Withdrawals due to AEs not reported.	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. Data from the first phase was not reported separately.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
McRae-Clark 2010 US	Adults between 18 and 65 years meeting DSM-IV criteria for marijuana dependence. Participants had to meet DSM-IV criteria for ADHD with the exception of the criterion that the age of onset of symptoms had to be prior to 7 years of age.	A. Atomoxetine 25 -100 mg/d B. Placebo Treatment period: 12 weeks	NR	Age, mean 29.9 (SD 10.9) Male: 80% Caucasian: 91%	WRAADs total score, mean (SD): 29.9 (6.4) Self reported CAARS, mean (SD): 44.3 (10.6) CGI-S, ADHD symptoms, mean (SD): 4.7 (0.7) % days of time-line follow-back with reported use: 85.9% Amount using per using day, prior 90 days, mean (SD): 4.0 (2.8) HDRS, mean (SD): 6.2 (3.9) HARS, mean (SD): 8.1 (5.3)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
McRae-Clark 2010 US	78	62/16/38	Atomoxetine vs placebo (p values are vs placebo) <u>Marijuana dependence</u> Estimated (LS mean) wk 12 self reported use: 2.17 (SE 0.34) vs 1.84 (0.34), p=0.44 % days reporting use , mean (SD): 60.1% (31.5%) vs 68.1% (31.3%), p=0.46 % days reporting use(self reported), mean (SD): 60.1% (31.5%) vs 68.1% (31.3%), p=0.46 % reduced days using relative to baseline: 84.2% vs 68.4%, p=0.45 % reduced amount using per using day relative to baseline: 73.7% vs 84.2%, p=0.69 CGI-I rating , LOCF, mean (SD)2.84 (1.12) vs 2.95 (1.08), p=0.65 CGI-S change from baseline, mean (SD): -1.28(1.23) vs -1.33 (1.46), p=1.00 Marijuana craving questionnaire change from baseline: -13.39(13.28) vs -17.05 (15.97), p=0.56 <u>ADHD</u> WRADDS change from baseline and longitudinal, mean (SD): -15.05 (10.96) vs -11.05 (7.59), p=0.23 CAARS-self, change from baseline and longitudinal: -12.65 (7.60) vs -10.16 (7.73), p=0.34 CGI-I rating, LOCF , mean (SD)2.63 (0.68) vs 3.26 (0.93), p=0.02 CGI-S change form baseline, mean (SD: -1.22 (0.94) vs -0.89 (1.28), p=0.21 Heavy use=6 standard marijuana units Median % of study days with heavy use : 0%, IQR 0% to 1.2% vs 2.1% IQR 0% to 6.0%, p=0.46 % of subjects with no heavy use on study: 68% (13/19) vs 47% (9/19), p=0.32

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
McRae-Clark 2010 US	Atomoxetine vs placebo, %, RR, 95% CI At least 1 AE: 100% vs 84%,1.19 (0.98 to 1.44) Anxiety/depression: 16% vs 11%, 1.50 (0.28 to 7.99) Headache: 37% vs 26%, 1.40 (0.54 to 3.64) Increased urination: 0% vs 11% Insomnia: 0% vs 21% Irritability: 11% vs 5%, 2.00 (0.20 to 20.24)	Atomoxetine vs placebo Total withdrawals: 82.1% vs 76.9% Withdrawals due to AE: 0% vs 0%	Grants R21DA18221, K23DA15440, K24DA00435 from the National Institute of Drug Abuse , Bethesda, MD	Of the 62 who withdrew, 32 did not receive any study medication and were excluded after randomization

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Medori 2008 Europe	Ages 18-65, chronic symptomology from childhood to adulthood with some symptoms present before age 7. Diagnosis of ADHD (DSM IV criteria) and confirmed by Conners' Adult ADHD Diagnostic interview. CAARS total score of ≥ 24 at screening.	Four treatment groups: PR Methylphenidate 18 mg once daily X 5 weeks PR Methylphenidate 36 mg once daily X 5 weeks PR Methylphenidate 72 mg titrated from 36 mg/ day for 4 days, 54 mg/ day for 3 days, 72 mg day X 4 weeks placebo once daily X 5 weeks	Stable dosage of antidepressant therapy for patients on therapy for 3 mo ≤. MOIs not allowed.	Mean age 34.0 54.4% male 97.5% white 2.5% other	Mean age at diagnosis: 29.9 Adult ADHD subtype: combined type 70.8% predominantly inattentive 24.2% predominantly hyperactive-impulsive 4.0% Alcohol / substance use disorders currently active .7% history not active 13.5% Mood and anxiety disorders currently active: 12% history and not active: 29.9%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Medori 2008 Europe	402	total withdrawn: 7 loss to fu: NR Analyzed 95/99/101/99 Efficacy: N=394 Safety: N=401	Mean change in CAARS:O-SV (compared with baseline) N=493 placebo -7.6 (CI -9.63; -5.59); MPH 18 mg -10.6 (P=.015); MPH 36 mg -11.5 (P=.013); MPH 72 mg -13.7 (P<.001) (no sig. between MPH groups) CAARS: O-SV >30% reduction Placebo 27.4%; MPH 18 mg 50.5%; MPH 36 mg 48.5%; MPH 72 mg 59.6% (P< .001) (no sig. between MPH groups) Mean change in CAARS:S-S (compared with baseline) Placebo -5.8 (CI -8.14; -3.45); MPH 18 mg -10.4 (P=.003); MPH 36 mg -11.3 (P=.003); MPH 72 mg -14.4 (P<.001) Mean change in CGI-S from baseline (N=388) placebo -.5 (CI -.69; -.32); MPH 18 mg -.9 (P=.003); MPH 36 mg -.9 (P=.005); MPH 72 mg -1.2 (P<.001) Mean change in SDS (N=304) placebo -2.2 (CI -3.08; -1.27); MPH 18 mg -4.8 (P=.008); MPH 36 mg -4.1 (P=.NS); MPH 72 mg -5.1 (P=.004)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Medori 2008 Europe	Adverse event > 3% total (top 10 events listed) placebo; MPH (18 mg, 36 mg, 72 mg) Decreased appetite: placebo 7.3%; 18 mg 19.8%; 36 mg 21.6%; 72 mg 34.3% Headache: placebo 17.7%; 18 mg 25.7%; 36 mg 20.6%; 72 mg 16.7% Insomnia: placebo 7.3%; 18 mg 11.9%; 36 mg 11.8%; 72 mg 16.7% Nausea: placebo 4.2%; 18 mg 7.9%; 36 mg 15.7%; 72 mg 14.7% Dry mouth: placebo 2.1%; 18 mg 7.9%; 36 mg 6.9%; 72 mg 20.6% Dizziness; placebo 7.3%; 18 mg 5.9%; 36 mg 9.8%; 72 mg 8.8% Weight decreased: placebo 5.2%; 18 mg 3%; 36 mg 7.8%; 72 mg 10.8% Nasopharyngitis: placebo 9.4%; 18 mg 6.9%; 36 mg 7.8%; 72 mg (3.9%) Tachycardia: placebo 0; 18 mg 4%; 36 mg 4.9%; 72 mg 7.8% Irritability: placebo 1%; 18 mg 4%; 36 mg 3.9%; 72 mg 8.8% Cardiac (placebo vs. PR methylphenidate 75 mg) Systolic BP ≥ 140 mm Hg: placebo 15.8% baseline, 19.3% week 5; PR MPH 13.9% baseline, 21.2 week 5 Diastolic BP ≥ 90 mm Hg: placebo 25.3% baseline, 15.9% week 5; PR MPH 18.8% baseline, 27.1% week 5 Pulse ≥90 bpm placebo 3.2% baseline, 5.7% week 5; PR MPH 1% baseline, 14.1% week 5.	Total withdrawals NR Withdrawals due to AE (n=13 4.3%) placebo 1%; 18 mg 1%; 36 mg 3.9%; 72 mg 7.8%	Janssen Pharmaceutica N.V.; Belgium	Withdrawals, loss to follow up not reported.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Michelson 2003/ Reimherr 2005/Faraone 2005/Spencer 2006 North America (Fair)	Adults who met DSM-IV criteria for ADHD as assessed by clinical interview and confirmed by the Conners' Adult ADHD Diagnostic Interview were recruited from clinics and by advertisement. Patients were required to have at least moderate symptom severity, and the diagnosis had to be corroborated by a second reporter for either current symptoms (by a significant other) or childhood symptoms (by a parent or older sibling).	Atomoxetine mean dose 94.4 mg/day; administered in evenly divided doses in the morning and late afternoon/early evening, beginning at 60 mg/day. Patients with residual symptoms had dose increased to 90 mg/day after 2 weeks, and to 120 mg/day after 4 weeks. Placebo Duration 10-week	NR	Mean age 40.2 63.6% male Ethnicity NR Mean age 42.1 66.4% male Ethnicity NR	Study I / Study II, ADHD subtype: Combined 71.8% / 60.5% Inattention 27.5% / 35.1% Hyperactive/Impulsive 0.7% / 4.3%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes

Michelson 2003/ Reimherr 2005/Faraone 2005/Spencer 2006 North America (Fair)	Study I: 280
	
	Study II: 256
		71 (25%) withdrew; 22 (7.8%) lost to FU; 267 (95%) analyzed (atomoxetine n=133, placebo n=134)
		
		79 (30.9%) withdrew; 12 (4.7%) lost to FU; 248 (96.9%) analyzed (atomoxetine m=124, placebo n=124)
			Mean change in score, atomoxetine vs placebo, Study I // Study II:
			CAARS-INV total ADHD symptom score -9.5 vs -6.0 (p=0.005) // -10.5 vs -6.7 (p=0.002)
			CAARS-INV Inattentive -5.0 vs -3.1 (p=0.010) // -5.8 vs -3.5 (p=0.001)
			CAARS-INV Hyperactive/Impulsive -4.5 vs -2.9 (p=0.017) // -4.7 vs -3.2 (p=0.013)
			CAARS-Self total ADHD Symptom score -16.0 vs -9.3 (p=0.002) // -17.3 vs -11.6 (p=0.008)
			CAARS-Self inattentive -15.9 vs -8.6 (p<0.001) // -12.5 vs -8.8 (p=0.025)
			CGI-ADHD-S -0.8 vs -0.4 (p=0.010) // -0.9 vs -0.5 (p=0.002)
			WRAADDS -5.3 vs -2.9 (p=0.002) // -4.5 vs -2.8 (p=0.041)
			HAM-D-17 -0.3 vs -0.6 (ns) // +0.2 vs -1.0 (p=0.013)
			HAM-A -1.0 vs -1.2 (ns) // -0.7 vs -1.0 (ns)
			Sheehan Disability total -4.5 vs -2.9 (p=0.022) // -4.4 vs -4.0 (ns)
			Sheehan Disability work life -1.6 vs -1.0 (p=0.007) // -1.8 vs -1.2 (ns)
			Sheehan Disability family life -1.5 vs -1.0 (ns) // -1.4 vs -1.6 (ns)
			Sheehan Disability social life -1.3 vs -0.9 (ns) // -1.2 vs -1.2 (ns)
			
			Spencer 2006 subanalyses of effects of comorbidities
			Predictor of outcome specific to atomoxetine on CAARS subscales: t test/df/p-value
			Investigator-rating Index Subscale:
			Depression NOS: 1.6/494/.121
			MDD: -2.2/500/.028
			Investigator-rating Hyperactivity subscale:
			Depression NOS: 3.9/494/.051
			MDD: -2.1/500/.033
			PTSD: -2.3/505/.020
			Self-rating Hyperactivity Subscale
			PTSD: 3.3/424/.069
			Depression NOS: 2.0/415/.049
			Investigator-rating Inattention subscale
			Depression NOS: -2.1/495/0.35
			PTSD: -2.2/505/.031
			Investigator-rating Total Score
			Depression NOS: 2.2/495/.028
			MDD: -2.0/500/.046
			PTSD: -2.4/505/.016
			Self-rating Total Score
			PTSD: 1.8/422/.069
			Depression NOS: 2.0/413/.045

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Michelson 2003/ Reimherr 2005/Faraone 2005/Spencer 2006 North America (Fair)	Atomoxetine vs placebo Dry mouth 21.2 vs 6.8% (p<0.001) Insomnia 20.8 vs 8.7% (p<0.001) Nausea 12.3 vs 4.9% (p=0.003) Decreased appetite 11.5 vs 3.4% (p<0.001) Constipation 10.8 vs 3.8% (p=0.002) Libido decreased 7.1 vs 1.9% (p=0.006) Dizziness 6.3 vs 1.9% (p=0.015) Difficulty attaining or maintaining erection (among males) 9.8 vs 1.2% (p<0.001) Sweating 5.2 vs 0.8% (p=0.004)	Atomoxetine vs placebo: Total withdrawals: 73 (27%) vs 55 (20.7%), (ns) Withdrawals due to AEs: 23 (8.5%) vs 9 (3.4%), (p=0.03)	Eli Lilly	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Paterson 1999 Australia (Fair)	Patients were eligible if they reported the presence of at least 4 inattentive and/or 5 hyperactive symptoms during the previous 6 months. Screening for illicit substance use among eligible patients was conducted by urinalysis.	Dexamphetamine mean dose 4.77 tablets per day (23.85 mg/day); Placebo. Dose was titrated gradually throughout the study. Week 1: 1 tablet in AM, Week 2: 1 tablet in AM and 1 tablet at noon, Week 3: 1 tablet in AM and 2 tablets at noon, Weeks 4-6: up to 6 tablets per day, but increased by no more than 1 tablet per day, with 2 days between increases. Duration 6 weeks	NR	Mean age 35.5 60% male Ethnicity NR	51% were inattentive type 46.7% were combined inattentive and hyperactive types 2% were hyperactive type
Reimherr 2007	Adults (18-65 yrs) with current diagnosis of ADHD using DSM-IV with at least moderate symptoms	Osmotic release oral system methylphenidate (OROS MPH) vs. placebo, titrated up from 18 mg per day until response w/ maximum dose of 90 mg per day. 2 arms 4 weeks each	NR	Age 30.6 Male 66% Ethnicity NR	#(%) ADHD alone 8(17) ADHD + Emotional dysregulation 18(38) ADHD +ED+ODD 19(40)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Paterson 1999 Australia (Fair)	45	1 (2.2%) withdrawn 0% lost to followup 45 (100%) analyzed: Dexamphetamine n=24, Placebo n=21	Mean change in score from 0 to 6 weeks, p-values signifying change from baseline, dexamphetamine vs placebo: ADHD score, Hyperactive -2.0 (p=0.004) vs -1.0; Inattentive -3.83 vs -1.57 (ns); Total -5.83 (p<0.0001) vs -3.57 (p=0.042) BSI mean T-score, Anxiety -8.2 (p<0.001) vs -5.43 (p<0.001); Depression -3.59 (ns) vs -2.76 (ns); Global Severity Index -5.5 (ns) vs -6.19 (ns) Efficacy Index at week 6: 95% of placebo had equal levels of benefits and side-effects; 75% of dexamphetamine had greater benefits than side-effects (p<0.001)
Reimherr 2007	47	6/NR/43-safety 41-efficacy	Mean total WRAADS score decrease Placebo 13% vs 42% OROS MPH P < 0.001 Mean total ADHD-RS score decrease Placebo 14% vs 41% OROS MPH P = 0.003

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Paterson 1999 Australia (Fair)	Dexamphetamine vs placebo, number of patients: Sleep disturbance: 9 vs 1 Headache: 6 vs 3 Dry mouth: 7 vs 0 Thirst: 3 vs 0 Mean weight loss: -3.6 kg (p<0.001) vs -0.286 kg (ns)	Dexamphetamine vs placebo, Total withdrawals: 1 (4.2%) vs 0% Due to AEs: 1 (4.2%, depression) vs 0%	Health Department of Western Australia	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.
Reimherr 2007	Placebo/ OROS MPH Mean weight change lbs 1.3 / -2.5 Decreased appetite 0/5 Sleep/insomnia 3/9 Anxiety 0/4 Subjects w/ at least 1 AE 39% / 55% at moderate impairment 23% / 39%	By treatment NA Total withdrawals 6 due to AEs NR	McNeil Pediatrics	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Rosler 2009 Germany	Outpatients >18 years of age who met diagnosis of ADHD using DSM-IV-TR criteria established by psychiatric expert. German short version of the Wender Utah rating scale (WURS) was used to make sure that childhood ADHD symptoms were present by a retrospective self report of the patient. Subjects needed a WAARDS score of ≥ 28 points to be included in the study.	MPH ER (50% MPH IR and MPH 50% ER) bid morning and afternoon dose. 10 mg/day titrated 5 weeks up to 60 mg/day depending on efficacy and tolerability. Mean daily dose .55 mg/ kg. X24 weeks total	NR	Mean age: MPH 35.2; Placebo 33.8 50% male	ADHD-DC score inattention: 7.7% hyperactivity/impulsivity: 7.1% other characteristics: WRAADS score at baseline: MPH ER 44.8; placebo. 45.5 CAARS-S:L DSM-IV ADHD total score at baseline: MPH ER 119.2; placebo. 117.9 CGI severity of illness at baseline: MPH ER 5.0; placebo. 5.1 Age at ADHD diagnosis:5.75 yrs

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Rosler 2009 Germany	363	MPH ER 58(24%); placebo 52(43%) lost to FU: MPH ER 12 (5%); placebo 11(9%) analyzed per drug: MPH ER 241; placebo 118	WAARDDS total effect size on the primary outcome was 0.39. Paired Wilcoxon-Test, P=0.004 (maintenance phase week 6 - week 24). WAARDDS > 30% reduction by week 24: 61% MPH ER vs. 42% placebo (P=0.001) CAARS-DATS: at week 24 difference was statistically significant (P=0.016) in favor of MPH ER (data not reported). Effect size=0.028 CGI ratings of vast and decided improvement regarding therapeutic effect MPH ER =60.1%; placebo=38.1% (P=0.0003)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Rosler 2009 Germany	Adverse events MPH > placebo decreased appetite 38 vs. 13% dry mouth 30 vs. 16% difficulties falling asleep 25 vs. 18% palpitations 23 vs. 19% excessive thirst 24 vs. 12% menstrual difficulties 11 vs. 0% reduced libido 11 vs. 3% hyperhidrosis 12 vs. 1% hot flashes 10 vs. 5% diarrhea 9 vs. 4% seborrhea 8 vs. 2% breathing difficulties 8 vs. 1% tremor 7 vs. 0% cardiac pain 7 vs. 1% blurred vision 5 vs. 1% paresthesia 4 vs. 0% nausea 9 vs. 3% <u>Adverse events placebo > MPH ER</u> drowsiness 47 vs. 30% shortened sleep 26 vs. 15% gastric discomfort 26 vs. 15% excessive appetite 16 vs. 10% chills 14 vs. 9% heaviness in legs 13 vs. 5% micturition difficulties 5 vs 1% vomiting 2.6 vs. .4%	MPH ER 58 (24%); placebo 52 (43%) withdrawals due to AE MPH ER 31 (13%); placebo 10 (8%)	Medice	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Schubiner 2002 US (Fair)	Between the ages of 18 and 55 years; DSM-IV criteria for current cocaine dependence; provide a urine specimen with a positive urine toxicology result for cocaine metabolite; meet criteria for the diagnosis of ADHD as a child and as an adult	Methylphenidate 30 mg/day for first 2 or 3 days; 60 mg/day for the next 4 to 5 days; 90 mg/day by day 8 Placebo Plus twice-weekly cognitive-behavioral group therapy (CBT) for cocaine dependence Pemoline arm dropped after the first year because of recruitment difficulties Dosing: three times daily (times nr) Duration: 13 weeks	NR	Mean age=37.5 89.6% male 70.8% white	No. days using cocaine in last 30 days=13.52 No. hyperactive symptoms=5.8 No. inattentive symptoms=4.8 Mean BDI scores=22.4 ASI Drug use=0.2242 Alcohol use=0.1605 Illegal activity=0.1172 Medical condition=0.1080 Family relations=0.3047 Psychiatric status=0.3324 Employment=0.4503 Affective disorders=56% Anxiety disorders=12.5% Other Axis I disorders=4.1%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Schubiner 2002 US (Fair)	59	34 (57.6%) withdrawn; 11 (18.6%) dropped due to being in the pemoline group; Lost to fu NR; 48 (100% for MPH vs placebo comparison) for most efficacy measures MPH n=24, placebo n=24	MPH vs placebo (mean change); differences NS unless otherwise specified No. inattentive symptoms=2.13 (-2.79) vs 2.83 (-1.96) No. hyperactive symptoms=3.42 (-2) vs 4.78 (-1.47) No. days using cocaine in past 30 days=15.42 (+2.13) vs 14.58 (+0.83) Amount spent on cocaine in past 30 days=$62.54 vs $97.19 Longest continuous abstinence=5.17 vs 5.17 % Urine samples tested negative for cocaine=0.5 vs 0.42 Physician efficacy ratings showing moderate improvement: 77% vs 21%, p<0.05 at 4 weeks: 77% vs 44% at 8 weeks: 60% vs 36% at 12 weeks: 50% vs 56% last visit: 73% vs 42%, p<0.05 Mean participant efficacy ratings at last visit: 1.88 vs 2.68; p<0.05 at 4 weeks: 2.57 vs 3.00 at 8 weeks: 2.08 vs 3.08 at 12 weeks: 1.75 vs 2.64

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Schubiner 2002 US (Fair)	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%)	Methylphenidate vs placebo: Total withdrawals: 13 (54.2%) vs 10 (41.7%) Withdrawals due to adverse events: 0 vs 1 (4.2%)	National Institute on Drug Abuse Grant R01 DA 10271-03 and a Joe Young Srs. Research grant from the State of Michigan	Comorbid for cocaine dependence Pemoline arm dropped (n=11) due to low enrollment after 1 year

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Spencer 1995 US (Fair)	Male or female aged 18-60, with at least 8 of 14 DSM-III-R criteria for ADHD (assessed by psychiatric evaluation and structured diagnostic interview), with onset in childhood by age 7, chronic course until time of assessment, and associated with significant distress and disability. Adults were self-referred or referred by other clinicians for life-long histories of inattention and underachievement.	Randomized crossover design of methylphenidate vs placebo, with 1 week washout between treatment phases; total trial duration 7 weeks. Study medication was titrated up to 0.5 mg/kg per day by week 1, 0.75 mg/kg/day by week 2, and up to 1.0 mg/kg/day by week 3.	NR	Mean age 40 43.5% male 100% white non-Hispanic	74% had at least one past comorbid psychiatric disorder 56% had a current comorbid psychiatric disorder
Spencer 1998 US (Fair)	Adults whom met full DSM-III criteria for ADHD by the age of 7 yrs, , with current, chronic symptoms, and endorsed impairment with the disorder.	Tomoxetine vs placebo. Patients randomized to Tomoxetine 40 mg/day in week 1, and 80 mg/day in weeks 2 and 3; or placebo.	NR	n=21 Adults aged 19-60 yrs, 11 women, 10 men, ethnicity NR.	1 lifetime comorbid psychiatric disorder (n=13) current ratings of severe depression or anxiety (n=2) family history of ADHD (n=20) average to above-average intelligence (n=21).

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Spencer 1995 US (Fair)	25	2 (8%) withdrawn 0% lost to followup 23 (92%) analyzed. N per drug in 1st treatment phase not reported.	Mean change in score during first treatment phase (Weeks 1-3), methylphenidate vs placebo: ADHD Rating Scale -18 vs -2.5 (p<0.0001) Global Severity subscale of the CGI Scale -1.8 vs 0 (p<0.0001) Mean change in ADHD symptom cluster score, using 1st and 2nd treatment phases combined, methylphenidate vs placebo: Hyperactivity overall -1.2 vs -0.16 (p<0.001) Impulsivity overall -1.3 vs -0.44 (p<0.001) Inattentiveness -0.62 vs -0.26 (p<0.001) % of patients who improved, i.e.. CGI score <2 and reduction >=30% in individual rating score: 78% vs 4% (p<-0.001)
Spencer 1998 US (Fair)	22	1 withdrawn/ 0 lost to FU 21 analyzed Tomoxetine: n=11 Placebo: n=10	Decrease in ADHD symptoms: tomoxetine: (11/21 subjects)-- week 2: p< 0.01; week 3: p<0.001 (3 week study) placebo: (2/10 subjects). **Results from scales and tests at end of study** reported as: paired tests of tomoxetine scores vs placebo scores; p-value McNemar test: (x= 7.4, df=1; p<0.01) Stroop Color Word test: (z=2.6, n=21, p<0.05) Interference T test scores: (z=2, n=21, p<0.05) ADHD rating scale: p-value= ns Parallel-groups comparison during the first 3 weeks of protocol (z= 3.2, n=21, p<0.01)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Spencer 1995 US (Fair)	Loss of appetite 26% Insomnia 22% Anxiety 22% Methylphenidate vs placebo: Mean heart rate 80 vs 76 beats/min (p<0.05) Mean weight 73.2 vs 74.3 kg (p<0.05)	Methylphenidate vs placebo, Total withdrawals 2 (8%) vs 0%; Withdrawals due to AEs: 2 (8%, chest pain in 1, agitation/irritability in another) vs 0%	NR	Outcomes from the first phase of treatment (MPH vs placebo) are presented separately, but number of patients in each group is not reported.
Spencer 1998 US (Fair)	no serious adverse events observed, 1 subject withdrawn after becoming very anxious on tomoxetine.	tomoxetine: 1/21 (due to increased anxiety in patient) placebo: 0 withdrawals;	"Funded in part by Lilly Research Labs" and an NIMH grant	3 week study period.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Spencer 2001 US (Fair)	Outpatient adults with ADHD aged 19-60, satisfying full diagnostic criteria for DSM-IV ADHD based on clinical assessment confirmed by structured diagnostic interview. ADHD diagnoses, with onset in childhood by age 7, chronic course until time of assessment, and associated with significant distress and disability.	Each medication was prescribed bid, taken at 7:30 AM and 2:30 PM. Amphetamine mixture (Adderall) was titrated up to 20 mg/day by week 1, 40 mg/day by week 2, and 60 mg/day by week 3. Mean dose at end of week 3 was 53.7 mg/day at end of week 3 (1st drug phase) Placebo mean dose 59.3 mg/day at end of week 3 Randomized crossover design with 1 week washout between treatment phases; Total trial duration 7 weeks	NR	56% male Mean age 38.8 96% white	93% had at least 1 lifetime comorbid psychiatric disorder 67% had 1 or more first- or second-degree relatives with ADHD
Spencer 2005 US (Poor)	Subjects aged between 19 and 60 years recruited from clinical referrals and advertisements in the local media. Subjects had to satisfy full diagnostic criteria for DSM-IV ADHD based on clinical assessment and confirmed by structured diagnostic interview.	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.	Other psychoactive medications were not permitted	Mean age 37 58.2% male Ethnicity: NR	38% major depression 9% multiple (>2) anxiety disorders

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Spencer 2001 US (Fair)	30	3 (10%) withdrawals; 0% lost to FU; 27 (90%) analyzed. N per drug not reported	Mean change in ADHD rating scale during first treatment phase (Weeks 1-3), Adderall vs placebo: -12 vs +1 (p<0.001) Mean change in score, data combined from 1st and 2nd drug phases, Adderall vs placebo: Stroop Test: Word T-score +5.6 vs +4.0 ; Color T-score +5.0 vs +2.6; Color-Word T-score +1.4 vs +0.7; Interference T-score +1.2 vs +1.0 Rey-Osterrieth Complex Figure: copy organization -0.8 vs +0.1; copy accuracy +0.4 vs -0.1; delay organization +1.1 vs +1.5; delay accuracy +8.8 vs +9.5 CPT: number of hits +9 vs +7.8, number of omissions -7.9 vs -6.2; number late -1.39 vs -1.74 % of patients who improved, i.e., >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% Decrease in ADHD symptoms: tomoxetine: (11/21 subjects)-- week 2: p< 0.01; week 3: p<0.001 (3 week study) placebo: (2/10 subjects). Results from scales and tests at end of study reported as: paired tests of tomoxetine scores vs placebo scores; p-v
Spencer 2005 US (Poor)	146	36/NR/110 26(25%) in MPH; 10(24%) in placebo dropout	Methylphenidate vs placebo, CGI rated "much" or "very much" improved: 63(68%) vs 6(17%), p<0.001

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Spencer 2001 US (Fair)	Adderall vs placebo: Insomnia 37 vs 14.8% (ns) Loss of appetite 29.6 vs 11.1% (p=0.03) Anxiety 25.9 vs 14.8% (ns) Headache 11.1 vs 7.41% (ns) Agitation 22.2 vs 7.4% (p=0.05)	Adderall vs placebo: Total withdrawals: 0 vs 3 (10%) Withdrawals due to AEs not reported	Shire Richwood Pharmaceuticals; NIMH grant	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.
Spencer 2005 US (Poor)	Methylphenidate vs placebo, Life events: 2(2%) vs 0(0%), p=0.37 Psychiatric adverse events: 7(7%) vs 0(0%), p=0.085 Somatic complaints: 2(2%) vs 0(0%), p=0.37	Methylphenidate vs placebo, Total withdrawals 26 (25%) vs 10(24%); Withdrawals due to AEs: 11(11%) vs 0(0%)	NIMH and Novartis	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Tenenbaum 2002 US (Fair)	Patients with symptoms of ADHD, defined as either: (i) two of the primary subscales of the ADSA or (ii) both of the subscales of Barkley's ADHD Rating Scale. ADSA ratings were significant when subscale scores were ≥1.5 SDs above the mean. Ratings on Barkley's scale were significant according to age/gender normative scores per by Barkley & Murphy 1998. Diagnosis of ADD, combined type was determined using DSM-IV criteria, clinical interviews and standard rating scales. A significant other attended each of 3 assessment/baseline sessions to provide collateral information.	All study medications were administered quid, at morning, noon, 4PM, and evening. Methylphenidate (up to 45 mg/day) dosed as follows, with placebo given at evening dose: Day 1-2: 5 mg AM and 5 mg noon, placebo 4PM Day 3-4: 5 mg AM, 5 mg noon, 5 mg 4PM Day 5-7: 10 mg AM, 10 mg Noon, 5 mg 4PM Day 8-10: 10 mg AM, 10 mg Noon, 10 mg 4PM Day 11-13: 15 mg AM, 15 mg noon, 10 mg 4PM Day 14-21: 15 mg AM, 15 mg noon, 15 mg 4PM Pycnogenol was administered qid, to a total dosage of 1 mg/lb body weight. Placebo qid Duration of each treatment phase: 3 weeks (17 weeks total, including 1 week baseline phase, washout periods between treatment phases, and 3-week follow-up)	NR	Mean age 42 45.8% male 100% white	Not reported

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Tenenbaum 2002 US (Fair)	33	9 (27%) withdrawn due to non-compliance 0% lost to FU 24 (72.7%) analyzed, N per drug not reported (phases were combined in analysis).	Composite score effect size, self-reported data; other-reported data: Barkley's ADHD Rating Scale 0.18/ 0.13; Attention Deficit Scales for Adults 0.19/0.09 Copeland Checklist for Adult ADD 0.20/0.23; Barratt Impulsiveness Scale 0.25/other NA Conners' CPT 0.13/other NA; Brown ADD Scales 0.25/0.22 Mean change from baseline in MPH vs placebo [Cohen's d effect size] from self-reported data; from other-reported data: Barkley's Inattention: -2.75 vs -2.79 [-.02] ; -1.18 vs -1.57 [-.15] Barkley's hyperactivity: -1.79 vs -1.79 [.00] ; -.96 vs -1.35 [-.17] ADS: Attention-Focus: -7.10 vs -4.80 [.33] ; -2.50 vs -3.50 [-.16] Behavior-Disorganized Activity: -9.00 vs -7.80 [.13] ; -6.60 vs -5.80 [.08] Emotive Scale: -4.90 vs -5.10 [-.04] ; -3.50 vs -3.00 [.07] Copeland: Inattention/Distractibility: -15.10 vs -9.40 [.30] ; -1.90 vs -8.20 [-.40] Impulsivity Scale: -15.00 vs -11.20 [.21] ; -5.10 vs -7.80 [-.12] Overactivity/Hyperactivity: -8.40 vs -16.50 [-.42] ; -3.60 vs -7.90 [-.20] Underactivity: -12.50 vs -8.20 [.22] ; -4.80 vs -5.20 [-.03] Barratt : Total scale: -5.60 vs -6.00 [-.04] ; Other-reported data N/A Cognitive impulsiveness scale: -1.70 vs -1.40 [.10] ; Other-reported data N/A Motor impulsiveness: -3.00 vs -2.70 [.07] ; Other-reported data N/A Non-planning impulsivity :-.90 vs -2.00 [-.22] ; Other-reported data N/A CPT: Standard Error of Hit Rate: -1.27 vs -1.25 [.01] ; Other-reported data N/A SE of variability in reaction times: -.30 vs -1.89 [-.40] ; Other-reported data N/A Hit rate minus inter-stimulus interval change: -.01 vs -.01 [.10] ; Other-reported data N/A Intertrial interval: -.01 vs -.01 [-.02] ; Other-reported data N/A Brown: Total score: -15.60 vs -15.10 [.02] ; -12.80 vs -18.80 [-.35] Activating and organizing to work: -3.60 vs -3.30 [.05] ; -3.80 vs -3.80 [-.15] Sustaining attention and concentration: -3.90 vs -3.30 [.13] ; -2.70 vs -4.70 [-.34] Sustaining effort and energy: -3.60 vs -3.20 [.07] ; -2.70 vs -3.80 [-.21] Managing affective interference: -2.13 vs -2.67 [-.14] ; -1.80 vs -2.30 [-.13] Utilizing working memory and accessing recall: -2.30 vs -2.70 [-.09] ; -2.00 vs -3.30 [-.41] Beck Depression: -1.68 vs -3.68 [-.31] ; Other-reported data N/A Beck Anxiety: .12 vs -2.17 [-.54] ; Other-reported data N/A Average effect size [-.02]; [-.18]

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Tenenbaum 2002 US (Fair)	NR	Methylphenidate vs placebo: Total withdrawals unclear by treatment group. Withdrawals due to AEs 0 vs 0	Henkel Corporation	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 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Turner 2004 UK (Fair)	DSM-IV diagnosis of ADHD; DSM-IV ratings from patient and/or informant of predominantly inattentive type and/or hyperactive-impulsive type during childhood and previous 6 months, and judgment by a consultant psychiatrist that patients' symptoms interfered with ability to function and were not explained by another disorder. Patients were also assessed by the GSI.	Modafinil single oral dose of 200 mg Lactose placebo, single oral dose 10 subjects were randomized to receive a single oral dose of lactose placebo first, followed by single dose of modafinil in the second session; the time of day that the dose was administered was not reported. 10 subjects were randomized to receive the drug first, followed by placebo. The single-dose treatment sessions were separated by one week. Duration: 1 week	NR	Mean age 28 65% male Ethnicity NR	Mean NART score 108 Mean GSI score 1.6 Mean education 13.5 Subjects were matched for age, NART verbal IQ, education level, and GSI, previous use of stimulant medication, current use of stimulant medication

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Turner 2004 UK (Fair)	20	Withdrawn NR Lost to followup NR 20 (100%) analyzed Analysis of 1st treatment phase included 10 in modafinil, 10 in placebo	Mean score among outcomes with significant drug x order interactions, on which a between-subjects analysis for the first session only was performed, modafinil vs placebo: Immediate PRM % correct 91.25 vs 91.25 (ns) DMTS % correct 87.50 vs 79.80 (p=0.016) SSP span length 6.50 vs 6.35 (ns); total errors 53.65 vs 55.10 (ns) NTOL latency (all moves) 19126 vs 15351 ms (p=0.004) RVIP target sensitivity (A') 0.937 vs 0.926 (ns) Mean scores on other tests, on which data from both sessions was combined, modafinil vs placebo: Digit span forwards score: 9.45 vs 8.00 (p<0.001); backwards score 8.35 vs 7.00 (p=0.017) Immediate PRM response latency 1889 vs 1714 ms (ns) Delayed PRM % correct 8735 vs 79.8 (p=0.016); response latency in ms 2340 vs 1769 (ns) PAL 1st trial memory score 16.7 vs 15.8 (ns); total errors 9.25 vs 9.95 (ns); total trials 8.1 vs 8.65 (ns) DMTS latency 5057 vs 4121 ms (ns) SWM strategy score 29.5 vs 30.1 (ns); between errors 17.35 vs 19.8 (ns); within errors 1.3 vs 1.35 (ns) NTOL mean attempts (all moves) 7.22 vs 7.86 (p=0.009) RVIP mean latency 439 vs 434 ms (ns); response bias (B") 0.83 vs 0.97 (ns) IDED total errors 24.4 vs 22.4 (ns); total reversal errors 12.2 vs 12.9 (ns); total EDS errors 7.7 vs 4.9 (ns) Gamble probability of choosing most likely outcome 0.92 vs 0.91 (ns); % bet (average) 58.7 vs 57.44 (ns); deliberation time 2473 vs 2244 ms (ns) STOP go reaction time 444 vs 420 ms (ns); go reaction time variability 137 vs 124 (ns); stop-signal reaction time 150.1 vs 172.7 (p=0.028); errors 5.7 vs 3.0 (ns)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Turner 2004 UK (Fair)	NR	Modafinil vs placebo, Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0	Wellcome Trust Program grant	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Turner 2005	Adult patient with ADHD who scored ≥172 on the attention-deficit scales for adults (ADSA) and who also were assessed with the Global Severity Index (GSI)	Methylphenidate 30 mg single dose and placebo. Dose given 75 minutes before testing started.	NR	Mean age (for n=18 patients with DSM-IV ADHD): 28.5 70.4% male (of original 27 patients; no data specified for smaller group)	Mean baseline GSI =1.4 (SD:0.6) 18 of 24 patients met DSM-IV criteria for ADHD; 5 of these had a diagnosis of "inattentive type" and 7 of "combined type". 6 of 24 patients did not meet DSM-IV ADHD criteria; they were classified as patients with "attentional difficulties" and were not included in the main analysis of the effects of MPH .

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Turner 2005	27	3 / NR / 24 (24 per drug)	No significant differences were seen between placebo and methylphenidate for the PRM, and the SSP, and none were seen for 3 of 4 parts of the SWM and for 1 of 3 parts of the RVIP. For the significant differences on the SWM, methylphenidate vs placebo: Between errors 6-box stage scores (SD) were: 2.3 (3.1) vs 6.8 (6.7), p = 0.0026 For the significant differences on the RVIP, methylphenidate vs placebo: Mean latency in milliseconds: 416.5 (67.7) vs 468.3 (85.1), p=0.006 Target sensitivity scores: 0.931 (0.006) vs 0.908 (0.06), p=0.026 On the VAS assessing patient's feelings, of the 16 different domains, the increases between methylphenidate vs placebo on these 7 feelings were significant: Alert, well-coordinated, contented, tranquil, quick-witted, attentive, interested

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Turner 2005	NR	3 enrolled patients did not have complete data, but no information was given about these patients.	Wellcome Trust Programme grant	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Verster 2008 Netherlands	Ages 21-55 with 6 ≤ of DSM-IV ADHD criteria of inattention and/or hyperactivity/impulsivity in childhood; 5 ≤criteria DSM-IV ADHD criteria of inattention and/or hyperactivity/impulsivity in adulthood; chronic persisting ADHD from childhood to adulthood; moderate to severe impairment due to ADHD. Driver's license 3 + years.	Prior to study participation participants were effectively treated with MPH. MPH regular dose (mean 14.7 mg) or placebo 1.5 hrs before driving test	NR	Mean age 38.3 61% male Ethnicity: NR	Baseline CAARS: 64.7 Baseline DSM attention index: 13.8 Baseline DSM hyperactivity index: 15.2 Baseline DSM ADHD index: 28.9 Mean years driving: 16.8 (range 3-30)
Weiss 2006	Outpatients age 18 to 66 years diagnosed ADHD via DSM IV	Placebo , Paroxetine (Par), Dextroamphetamine (Dex) and Par + ex, titrated for 4 weeks up to Par 40 mg/day and Dex 40 mg day Duration 20 weeks	No but all received psychotherapy	Mean age 37.5 64% male Ethnicity 85% white	53% lifetime mood or anxiety disorder

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Verster 2008 Netherlands	19	1 /10 MPH /0/9 placebo Lost to FU 0/18 9 MPH/ 9 placebo	SDLP (cm) (Weaving of car) mean scores: Placebo 21.1; MPH 18.8 (difference 2.3) P=0.004 Lateral position: NS SD speed (km/h): NS Mean speed (km/h): NS Self Reports of driving quality: Compared to placebo, MPH improved driving quality (P=0.023); mental effort while driving less for MPH (P=0.028) (data not available)
Weiss 2006	98	34/NR/98 Placebo 26 Par 24 Dex 23 Par + Dex 25	Response CGI-I Much or very much improved Placebo 28% Par 65.2% Dex 63.6% Par+Dex 56% Response CGI-I-ADHD Much or very much improved Placebo 16% Par 63.6% Dex 44% Par+Dex 44% Response CGI-I for mood and anxiety disorder Much or very much improved Placebo 36% Par 69.6% Dex 45.5% Par+Dex 48%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Verster 2008 Netherlands	NR	Placebo/ MPH 0/9; 1/9 0/18 withdrawals due to AE	Utrecht University	Blinding: 61.1% patients guessed which treatment they received at day 22 of 36 test days.
Weiss 2006	83% of patients reported at least one AE	Total withdrawals: Placebo 5 Par 9 Dex 9 Par+Dex 10 Due to AEs: Placebo 2 Par 6 Dex 3 Par+Dex 7	GlaxoSmithKline	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Wender 1985 US (Fair)	White patients aged 21-45 with prominent complaints of impulsivity, irritability restlessness, and emotional lability. Included patients whose mothers were available and willing to fill out the Parent Rating Scale, with IQ >90. Utah criteria for ADD, residual type; subject must first have had a history of ADHD in childhood as well as both hyperactivity and ADD persisting from childhood, and additionally have affective lability; inability to complete tasks; hot or explosive temper; impulsivity; and stress intolerance.	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.	NR	Mean age 31.1 54% male Ethnicity NR	Comorbidities: 68% dysthymic disorder 22% cyclothymic disorder

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Wender 1985 US (Fair)	37	0% withdrawn; 0% lost to followup; 37 (100%) analyzed, N per drug not reported (phases were combined in analysis).	Final physician and patient ratings, methylphenidate vs placebo: Physician's Global Rating scale 1.4 vs 0.16 (p<0.005) Global Assessment Scale 69.17 vs 61.26 (p<0.005) Physician's target symptom ratings (1=none, 4=marked): hyperactivity 2.33 vs 3.29 (p<0.005); short attention span 2.27 vs 3.35 (p<0.0005); mood problems 2.36 vs 3.14 (p<0.005); anger 2.35 vs 3.11 (p<0.01); disorganization 2.12 vs 3.03 (p<0.005); conduct disorder 1.42 vs 1.67 (ns) Patient's subjective experience (1=absent, 5=very much): nervous 2.56 vs 2.97 (ns); happy 3.16 vs 2.70 (p<0.05); energetic 3.27 vs 3.11 (ns); mind wandering 2.37 vs 2.97 (p<0.025); hot tempered 2.32 vs 2.43 (ns); calm 2.83 vs 2.35 (ns); sad 1.81 vs 2.10 (ns); tired/sleepy 1.88 vs 2.28 (ns); concentrating 2.86 vs 2.41 (ns); hungry 1.97 vs 2.51 (p<0.025); cool tempered 3.97 vs 2.44 (p<0.025); global 4.97 vs 4.31 (ns) Profile of mood states: tension-anxiety 49.06 vs 55.71 (p<0.001); depression-dejection 43.88 vs 50.50 (p<0.001); anger-hostility 50.34 vs 57.03 (p<0.01); vigor 70.40 vs 66.53 (ns); fatigue 48.00 vs 53.47 (p<0.05); confusion 51.53 vs 58.25 (p<0.001) BDI 8.94 vs 9.23 (ns)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wender 1985 US (Fair)	Mild anxiety, insomnia, jaw tension, tooth grinding, overstimulation, irritability, nose tingling	Methylphenidate vs placebo: Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0	NIMH grant	Data from the first phase was not reported separately. Outcomes were presented as combined data from phases of each drug.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Wernicke 2004 US (Fair)	Adults who met DSM-IV criteria for ADHD as assessed by clinical interview and confirmed by the Conners' Adult ADHD Diagnostic Interview (CAAR-D) were randomized to acute treatment (approx. 10 weeks) with atomoxetine or placebo in 2 identical double-blind studies.	Atomoxetine vs placebo. For patients randomized to atomoxetine, dose was initiated at 60 mg/day (30 mg bid), titrated based on clinical response to a maximum of 120 mg/day (60 mg bid). After approximately 10 weeks, a 4-week double-blind discontinuation phase. Atomoxetine patients were randomized to either abrupt or tapered discontinuation, in which dose was reduced weekly.	NR	NR NR NR	Not reported

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Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Wernicke 2004 US (Fair)	380	2 (0.5%) withdrawn; lost to FU NR; 377 (99.2%) analyzed (atomoxetine-abrupt discontinuation n=89, atomoxetine-tapered discontinuation n=93, placebo n=195)	Change in symptom severity from pretreatment phase to end of treatment phase :: from end of treatment phase to end of discontinuation phase, in atomoxetine abrupt discontinuation vs tapered discontinuation vs placebo: CAARS total score -11.2::5.1 vs -11.4::3.6 vs -7.0::2.7 (ns) HAM-A -0.5::-0.5 vs -1.8::0.2 vs -1.5::0.0 (ns) HAM-D 0.4::-0.5 vs -1.1::0.0 vs -0.9::0.4 (ns) During the discontinuation phase, changes in ADHD symptom ratings did not differ significantly between treatment groups. Depressive or anxiety symptoms did not significantly increase following drug discontinuation, compared with placebo.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wernicke 2004 US (Fair)	% in atomoxetine-abrupt vs atomoxetine-tapered vs placebo: Headache 4.4 vs 10.6 vs 4.1% (ns) Pain in limb 3.3 vs 1.1 vs 0% (p=0.019) Diarrhea 2.2 vs 5.3 vs 2.6% (ns) Sinusitis 2.2 vs 4.3 vs 0.5 (ns) Insomnia 1.1 vs 5.3 vs 3.1 (ns) Irritability 0 vs 4.3 vs 0% (p=0.007) Dyspepsia 0 vs 4.3 vs 0.5% (ns) Allergic reactions: 1.1 vs 6.5 vs 1.5% (p=0.036)	Atomoxetine-abrupt vs atomoxetine-taper vs placebo: Total withdrawals: 0 vs 1 (1%) vs 1 (0.5%) Withdrawals due to AEs: 1 (1%) in atomoxetine-taper discontinuation phase, due to headache	Eli Lilly	Depressive or anxiety symptoms did not significantly increase following drug discontinuation.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Wigal 2011 US	Otherwise healthy adults aged 18-55 years who satisfied the DSM-IV criteria for a primary diagnosis of ADHD and who had a baseline ADHD-RS-IV with adult prompts score ≥28.	A: Lisdexamfetamine dimesylate 30, 50, or 70 mg/d B: Placebo Two week crossover study (1 week for each phase). Before randomization, there was a 4 week dose-optimization phase, where participants started at 30 mg and increased until dosage was tolerable with AEs.	NR	Mean age: 30.5 (SD 10.70) years Male: 62% Caucasian: 89.4%	Mean (SD) BMI: 27.2 kg/m2 (5.02) Combined-type ADHD: 69.0% Predominantly inattentive type: 27.5% Mean (SD) ADHD-RS-IV with adult prompts total score at baseline: 37.0 (5.61)

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Wigal 2011 US	142	39/2/105 (ITT)	Lisdexamfetamine vs Placebo ADHD-RS-IV with Adult Prompts, LS Mean (SE) in the Crossover Phase: Total score: 18.1 (0.94) vs 29.6 (0.94); Difference in LS Mean: -11.5 (95% CI, -14.2 to -8.9), P<0.0001; LS Mean Model-Based Effect Size: -1.2 (SE 0.19) Inattention subscale score: 9.8 (0.50) vs 16.1 (0.50); Difference in LS Mean: -6.3 (95% CI, -7.7 to -4.9), P<0.0001; LS Mean Model-Based Effect Size: -1.2 (SE 0.19) Hyperactivity/impulsivity subscale score: 8.3 (0.53) vs 13.5 (0.53); Difference in LS Mean: -5.2 (95% CI, -6.6 to -3.7), P<0.0001; LS Mean Model-Based Effect Size: -1.0 (SE 0.17) Average total PERMP score from all post-dose assessments during the adult workspace environment sessions: P<0.0001 favoring lisdexamfetamine Lisdexamfetamine also demonstrated significant efficacy vs placebo at each post-dose time point from 2 to 14 hours based on total PERMP scores (P<0.0017). Overall LS mean (SE) model-based effect sizes for the average of all post-dose sessions were large for PERMP-A and PERMP-C (0.9 [0.17] and 0.8 [0.16], respectively). Least-squares mean model-based effect sizes for PERMP-A and PERMP-C were medium to large at all individual post-dose time points from 4 to 4 hours, and small to medium at 2 hours.

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wigal 2011 US	Dose-optimization phase (taking lisdexamfetamine): Participants with treatment-emergent AEs: 79.6% *Treatment-emergent AEs reported in ≥5% of participants:* Decreased appetite: 36.6% Dry mouth: 30.3% Headache: 19.7% Insomnia: 18.3% URTI: 9.9% Irritability: 8.5% Nausea: 7.7% Anxiety: 5.6% Feeling jittery: 5.6% Cross-over phase, Lisdexamfetamine vs Placebo: Participants with treatment-emergent AEs: 27.8% vs 35.9% *No treatment-emergent AEs were reported by ≥5% of participants receiving lisdexamfetamine during this phase of the study.* Fatigue: NR vs 12% URTI: NR vs 7.7% ***Note:*** Treatment emergent AEs that continued uninterrupted from dose-optimization phase to crossover phase without change in severity were counted only in the dose-optimization phase.	Lisdexamfetamine-Placebo group vs Placebo-Lisdexamfetamine group: *Discontinued prior to randomization (lisdexamfetamine dose-optimization phase):* Total withdrawals: 15 (10.6%) Due to AE: 4 (2.8%) *Crossover phase:* Total withdrawals: 11 (17.5%) vs 13 (20.3%) Due to AE: 0 (0%) vs 2 (3.1%) ***Note:*** Did not report during which treatment was being taken when the participant withdrawal took place, only whether they were in the group receiving lisdexamfetamine first or the group receiving placebo first.	Shire Development Inc.	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Wilens 2001 US (Fair)	Subjects were outpatient adults with ADHD aged 20-59, recruited from advertisements and clinical referrals to a psychopharmacology clinic. To obtain a full diagnosis of adult ADHD, the subject had to have 1) fully met the DSM-IV criteria for ADHD by age 7 as well as currently (within the past month); 2) described a chronic course of ADHD symptoms from childhood to adulthood, and 3) endorsed a moderate or severe level of impairment attributed to those symptoms.	Bupropion SR 200-400 mg/day, taken upon awakening and 6 hours later. Dose was titrated over 4 weeks, beginning at 100 mg bid, and increased by 100 mg weekly up to 200 mg bid in week 4. Bupropion mean dose at week 6: 362 mg/day. Weekly supplies of bupropion and placebo were dispensed in 100-mg capsules. Placebo mean dose at week 6: 379 mg/day Duration 6 weeks	NR	Mean age 38.3 55% male Ethnicity NR	Inattentive subtype 58% Combined subtype 35% Hyperactive or impulsive subtypes 8% Major depression: past 59%, current 19% Two or more anxiety disorders: past 19%, current 8% Substance abuse/dependence: past 35%, current 0% Smoking: past 33%, current 10% Alcohol abuse/dependence: past 33%, current 10% Antisocial personality disorder: past 16%, current 0%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Wilens 2001 US (Fair)	40	2 (5%) withdrawn; 0% lost to FU; 40 (100%) analyzed: Bupropion n=21, Placebo n=19	Bupropion vs placebo: CGI improvement rating of 1 (much improved) or 2 (very much improved): 52 vs 11%, p=0.007 Improved by 30% or more reduction in DSM-IV ADHD symptom checklist score: 76 vs 37% (p=0.02) Mean change from baseline to 6 weeks in ADHD symptom checklist score: -42% vs -24% (p=0.05) Proportion of the 18 DSM-IV ADHD-specific symptoms that improved: 100 vs 44% (p<0.001) Depression and anxiety (HAM-D, BDI, HAM-A): no difference between groups

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wilens 2001 US (Fair)	Bupropion vs placebo: Headache 19 vs 16% (ns) Aches or pains 10 vs 5% (ns) Dry mouth 10 vs 0% (ns) Chest pain 10 vs 0% (ns)	Bupropion vs placebo, Total withdrawals: 2 (9.52%, noncompliance) vs 0% Due to AEs: 0 vs 0	Glaxo Wellcome Inc.; NIH; National Institute on Drug Abuse	

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Winhusen 2010/ Covey 2010 US	Interested in quitting smoking, aged between 18 and 55 years and in good physical health. Vital sign criteria cut off was 15/85 mm Hg for blood pressure and 90 bpm for heart rate for the first 143 participants randomly assigned into trial. Patients aged ≥40 years, 130/80mm Hg and/or heart rate >88 bpm for the remainder of the trial, DSM-IV ADHD-RS total score>22; to smoke at least 10 cigarettes per day, to have a carbon monoxide level ≥8 ppm and to have smoked cigarettes for at least 3 mo.	A. OROS-Methylphenidate 18mg to72mg/d B. Placebo 11 wk treatment phase and 1 mo follow-up. Nicotine patches 21mg/d through wk 11, for tapering 14mg/d for weeks 12 and 13 , 7mg/d for wk 14	NR	Age: 38 years Male: 56% White: 82% African American: 6% Asian: 1.6% Native AmericaN/Alaskan :0% Other: 4% Mixed race: 5.6% Hispanic: 7.1%	Marital status Married: 34.1% Separated/widowed/divorced: 21.4 Never married: 44.5% Education: 14.4 years Employed full time/part time: 92.0% Lifetime psychiatric comorbidity Major depression:34.1% Bipolar disorder: 0% Anxiety disorder: 33.7% Substance use disorder: 60.8% DSM-IV ADHD rating scale score: 36.4% Adult ADHD subtype Inattentive: 34% Hyperactive-impulsive: 4% Combined: 61.9% Smoking history Fagerstrom score: 5.5 No. of smoking years: 19.7% No. of cigarettes/d; 19.8 No. of past quit attempts: 6.9%

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Winhusen 2010/ Covey 2010 US	255	51/27/255	OROS Methylphenidate vs placebo % of patients with prolonged abstinence: 43.3% vs 42.2%, x^2 =0.08, p=0.78 Cigarettes per d-a treatment X wk interaction effect for the post-quit phase: x^2=5.85, p=0.016 DSM-IV ADHD-RS Total score change from baseline at 11 weeks: -18 vs -11.7, p<0.0001, X2=15.93 % of patients with DSM-IV ADHD-RS total score reduction by 30%: 71% vs 44%, x2=15.56, p<0.001 Mean change from baseline at wk 11 in SBP (mmHg): 1.8 (10.0) vs 0.1 (8.3), at wk 13: 1.6 (10.3) vs 0.4 (8.9) treatment effect x2:5.22, p<0.05 Mean change from baseline at wk 11 in DBP(mmHg): 1.4 (7.0) vs -0.8 (6.2), at wk 13: 0.6 (7.2) vs 0.1 (7.1), treatment effect x2: 12.13, p<0.001 Mean change from baseline at wk 11 in heart rate (bpm): 2.2 (10.2) vs 0.6 (8.4), at wk 13 : 1.8 (10.8) vs 2.4 (11.0), treatment effect x2: 10.56, p<0.01 Proportion of patients with max. SBP of 140mmHg or greater: 16.7% vs 9.6%, x2 :2.74, p=0.10 Proportion of patients with max DBP of 140mmHg or greater: 20.6% vs 12.0%, x2=3.42, p=0.06 Proportion of patients with max heart rate of 100bpm or greater: 20.6% vs 15.2%, x2 1.26, p=0.26 <u>Abstinence (Covey 2010)</u> Complete abstinence: among non-whites: 42.9% vs 13.3%, x^2(1): 5.20, p=0.02 Complete abstinence among whites: 23.1% vs 23.5%, X^2(1): 0.00, p=0.95

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Winhusen 2010/ Covey 2010 US	OROS MPH vs Placebo Any TEAE: 96.1 vs 87.5%, p=0.01 TEAE related to study medications: 87.4% vs 74.2%, p=0.01 Any serious TEAE: 87.4% vs 74.2%, p=0.25 Nervousness: 22% vs 24% Anxiety: 18.9% vs 14.1% Insomnia: 17.3% vs 13.3% Depression: 5.5% vs 1.6% Headache: 27.6% vs 21.9% Dizziness: 6.3% vs 3.9% Nausea: 14.2% vs 7.8% Dyspepsia: 7.1% vs 0.8%, p=0.01 Fatigue: 11.8% vs 9.4% Cough: 8.7% vs 4.7% Decreased appetite: 18.1% vs 5.5%, p=0.00 Heart rate increase: 7.1% vs 0.8%, p=0.01 Palpitations: 7.1% vs 0.8%, p=0.01 Weight loss: 2.2 lb (SD 11.1) vs 2.1 lg SD 8.5) weight gain X2=42.91, p<0.0001	OROS MPH vs placebo Total withdrawals (includes DB treatment phase +follow-up phase): 18.9% vs 21.1% Withdrawals due to AE (Includes DB treatment phase +follow-up phase): 0% vs 0%	Grants from National Institute of Drug Abuse U10-DA015831 and K24 DA022288 to Harvard University U10-DA013035 to New York State Psychiatric Institute, U10-DA013046 to New York University, U10-DA013036 to Oregon Health and Science University and U10-DA013732 to the University of Cincinnati	No. withdrawn and lost to follow up includes those withdrawn during DB treatment phase as well as follow-up phase

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Wood 1976 (Fair)	Adults who had a rating, as children, of hyperactivity from parents' report (Conner Abbreviated Rating Scale) scoring over the 95th percentile, with prominent complaints of no change in adulthood.	Methylphenidate for 2 weeks twice daily, at variable, NR dose amounts, gradually increased to max of 60mg. Crossover: to methylphenidate, doses varying to 20-60 mg/day (specifics NR)of: Methylphenidate or Pemoline	Imipramine, 10mg, was used with 1 subject, who did not respond to Pemoline,	N=15 but only 11 in cross-over Age Range: 21-60 Ethnicity: Caucasian Male: 40% (of the 15 total)	RDC diagnoses: generalized anxiety disorder: n=8 cyclothymic disorder: n=4 drug/alcohol abuse: n=2 antisocial disorder: n=2 minor depressive disorder: n=4 N>15, as patients as patients over-lapped in these diagnoses

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes
Wood 1976 (Fair)	11	0/0/11 analyzed: NR	**Self-rating Responses of Double-Blind Trial (n=11) of Methylphenidate vs Placebo** Methylphenidate vs Placebo; p-Value Happy-Sad: 1.37 vs 2.66; p=NS 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

Evidence Table 7. Data abstraction of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wood 1976 (Fair)	No adverse effects reported, no response to meds: n=1	0/0	NR	

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Adler 2008 (Atomoxetine)	Method NR	Method NR	Yes	Yes	NR	NR	NR
Adler 2008 (Lisdexamfetamine)	Method NR	Method NR	Yes	Yes	Yes	NR	Yes
Adler 2009	Yes	Yes	Yes	Yes	NR	Yes	Yes
Adler 2009 ("Atomoxetine treatment in adults…")	Yes, computer algorithm	Yes, interactive voice response system	Unclear, declared no differences, but table of characteristics not provided	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind
Barkley 2007	Method NR	Yes	N/A (within group crossover design)	Yes	Yes	No	Yes
Biederman 2006	Method NR	Method NR	No, SS difference in age and ADHD onset	Yes	NR	NR	Yes
Bouffard 2003	No (numbers chosen from a hat)	No (see comment in Evidence Table)	NR by phase; same subjects exposed to both treatments	Yes	Yes but method not described	NR	Yes but method not described
Carpentier 2005	Method NR	Method NR	NR	Yes	NR	NR	Yes

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Intent-to-treat analysis; If No: % analyzed	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*
Adler 2008 (Atomoxetine)	Unclear	No	*Not rated*	High: Yes, (58%) Differential: no	Yes NR Yes NR
Adler 2008 (Lisdexamfetamine)	141 (98%)	No	*Not rated*	No/No 7 (2%)	Yes No NR No
Adler 2009	Yes	Yes, 3 patients randomized to MPH OROS failed to meet inclusion criteria and did not receive study medication.	*Not rated*	No/No	Yes NR Yes NR
Adler 2009 ("Atomoxetine treatment in adults…")	No, excluded 23% of randomized patients with a response > 25% during placebo run-in phase	*Not rated*	Unclear	*Not rated*	*Not rated*
Barkley 2007	NR	No	*Not rated*	No/No	Yes No No No
Biederman 2006	No 141/149 (95%) analyzed	No	*Not rated*	No/No	Yes NR NR NR
Bouffard 2003	No: 79%	No	*Not rated*	No/No	NR NR NR NR
Carpentier 2005	No 19/25 (76%) analyzed	No	*Not rated*	No/No	Yes NR NR NR

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? (*Update 4*)	Quality rating
Adler 2008 (Atomoxetine)	*Not rated*	*Not rated*	Fair
Adler 2008 (Lisdexamfetamine)	*Not rated*	*Not rated*	Fair
Adler 2009	*Not rated*	*Not rated*	Fair
Adler 2009 ("Atomoxetine treatment in adults…")	Unclear, Unclear, Unclear	Overall=No (41%) Between-group=Yes	Fair
Barkley 2007	*Not rated*	*Not rated*	Fair
Biederman 2006	*Not rated*	*Not rated*	Poor
Bouffard 2003	*Not rated*	*Not rated*	Fair
Carpentier 2005	*Not rated*	*Not rated*	Fair

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Chronis-Tuscano 2009	NR	NR	Yes	Yes	NR	NR	Stated blinding, but no details given
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	NR by phase; same subjects exposed to both treatments	Yes	Yes but method not described	NR	Yes but method not described
Kay 2009	NR	NR	Yes	Yes	NR	NR	Pills the same
Kinsbourne 2001	Method NR	Method NR	NR by phase; same subjects exposed to both treatments	Yes	Yes	NR	Yes
Konstenius 2010	Yes, Trombul software	Yes, hospital pharmacy	Unclear; age is 5 yrs different, and age at onset of amphetamine use is also 2.8 yrs different	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind
Levin 2001	NR	NR	NR	Yes	Yes	Yes	Yes
Levin 2006	Method NR	Method NR	Yes, except for employment status (significantly higher proportion of pts in bupropion group employed)	Yes	NR	NR	Yes
Levin 2007	Method NR	Method NR	Yes	Yes	NR	NR	Yes

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Intent-to-treat analysis; If No: % analyzed	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*
Chronis-Tuscano 2009	No: 87%	No	*Not rated*	No; 2/23	NR NR NR NR
Cox 2000	Yes	No	*Not rated*	No/No	Yes No No No
Gualtieri 1985	Yes	No	*Not rated*	No/No	Yes NR NR NR
Kay 2009	No, 3 subjects taken out in cohort 1	No	*Not rated*	No	NR NR NR NR
Kinsbourne 2001	Yes	No	*Not rated*	No/No	No No No Yes
Konstenius 2010	Yes	*Not rated*	Yes	*Not rated*	*Not rated*
Levin 2001	No	No	*Not rated*	NR	Yes NR NR NR
Levin 2006	Yes	No	*Not rated*	No/No	Yes NR NR NR
Levin 2007	Yes	No	*Not rated*	No/No	NR NR NR NR

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? (*Update 4*)	Quality rating
Chronis-Tuscano 2009	*Not rated*	*Not rated*	fair
Cox 2000	*Not rated*	*Not rated*	Fair
Gualtieri 1985	*Not rated*	*Not rated*	Fair
Kay 2009	*Not rated*	*Not rated*	fair
Kinsbourne 2001	*Not rated*	*Not rated*	Fair
Konstenius 2010	Unclear, Unclear, Unclear	Overall=No (29%) Between-group: No (placebo=16%, MPH=41%)	Fair
Levin 2001	*Not rated*	*Not rated*	Fair
Levin 2006	*Not rated*	*Not rated*	Fair
Levin 2007	*Not rated*	*Not rated*	Fair

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Marchant 2011	Unclear	Unclear	Unclear; no comparison of characteristics based on order of randomization to crossover design	Yes	Unclear; described as double-blind	Unclear; described as double-blind	Unclear; described as double-blind
Mattes 1984	Method NR	Method NR	NR by phase; same subjects exposed to both treatments	Yes	Yes but method not described	NR	Yes but method not described
McRae-Clark 2010	Unclear	Yes, central pharmacy	Unclear, baseline characteristics only compared between groups for the 38 patients (83%) who returned for at least one post-baseline assessment and comprised the modified ITT group	Yes	Yes for self-administered (CAARS-Self), unclear for others	Yes	Yes
Medori 2008	Yes	Yes	Yes	Yes	Described as double blind, but no details reported	NR	Described as double blind, but no details reported
Michelson 2003	Yes	Method NR	Yes	Yes	Yes	NR	Yes
Paterson 1999	Method NR	Method NR	Yes	Yes	Yes but method not described	NR	Yes
Reimherr 2007	Method NR	Method NR	Yes - there were some difference between groups but they did not reach statistical significance	Yes	NR	NR	Yes

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Intent-to-treat analysis; If No: % analyzed	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*
Marchant 2011	Unclear; reported that 65 (97%) furnished at least some double-blind data and that LOCF was used, but actual N's analyzed NR	*Not rated*	Unclear, reasons for noncompletion NR	*Not rated*	*Not rated*
Mattes 1984	No: 92%	No	*Not rated*	No/No	NR NR NR NR
McRae-Clark 2010	No, excluded 8 (17%) who didn't return for medication evaluation	*Not rated*	Unclear; somewhat higher Self Reported CAARS score in placebo group (46.9 vs 40.1, *P*= 0.06)	*Not rated*	*Not rated*
Medori 2008	No, excluded 7/401 (2%)	Yes	*Not rated*	No/No	Yes NR NR NR
Michelson 2003	No: 96%	No	*Not rated*	No/No	Yes No No No
Paterson 1999	Yes	No	*Not rated*	No/No	Yes NR NR NR
Reimherr 2007	No Efficacy analysis: 41/47 (87%) Safety analysis: 43/47 (91%)	No	*Not rated*	No/No	Yes Yes Yes Yes

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? (*Update 4*)	Quality rating
Marchant 2011	Unclear, Unclear, Unclear	Overall: No=22% Between-group: Unclear	Poor
Mattes 1984	*Not rated*	*Not rated*	Fair
McRae-Clark 2010	Unclear, Unclear, Unclear	Overall: No=65% Between groups: Yes	Poor
Medori 2008	*Not rated*	*Not rated*	Fair
Michelson 2003	*Not rated*	*Not rated*	Fair
Paterson 1999	*Not rated*	*Not rated*	Fair
Reimherr 2007	*Not rated*	*Not rated*	Fair

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Rosler 2009	NR	NR	Yes	Yes	NR	NR	NR
Schubiner 2002	NR	NR	No; MPH>placebo in ASI psychiatric composite scores	Yes	Yes	Yes	Yes
Spencer 1995	Method NR	Method NR	NR by phase; same subjects exposed to both treatments	Yes	Yes	NR	Yes
Spencer 1998	Method NR	Method NR	NR by phase; same subjects exposed to both treatments	Yes	NR	NR	Yes
Spencer 2001	Method NR	Method NR	NR 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	NR	Yes	Yes but method not described	NR	Yes
Turner 2004	Method NR	Method NR	Yes	Yes	Yes but method not described	NR	Yes but method not described
Verster 2008	Yes	Method NR	NR	Yes	NR	NR	Yes

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Intent-to-treat analysis; If No: % analyzed	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*
Rosler 2009	Yes	No	*Not rated*	No. MPH ER 5%; placebo 9%	NR NR NR NR
Schubiner 2002	Yes	No	*Not rated*	NR	Yes No No No
Spencer 1995	No: 92%	No	*Not rated*	No/No	Yes NR NR NR
Spencer 1998	No: 95.4%	No	*Not rated*	No/No	Yes NR NR NR
Spencer 2001	No: 90%	No	*Not rated*	No/No	Yes NR NR NR
Spencer 2005	No	No	*Not rated*	NR	Yes NR NR NR
Tenenbaum 2002	No: 72.7%	No	*Not rated*	No/No	Yes NR NR NR
Turner 2004	Yes	No	*Not rated*	No/No	Yes NR Yes NR
Verster 2008	No; 18/19 (94.7%) analyzed	No	*Not rated*	No/No	Yes NR NR NR

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? (*Update 4*)	Quality rating
Rosler 2009	*Not rated*	*Not rated*	Fair
Schubiner 2002	*Not rated*	*Not rated*	Fair
Spencer 1995	*Not rated*	*Not rated*	Fair
Spencer 1998	*Not rated*	*Not rated*	Fair
Spencer 2001	*Not rated*	*Not rated*	Fair
Spencer 2005	*Not rated*	*Not rated*	Poor
Tenenbaum 2002	*Not rated*	*Not rated*	Fair
Turner 2004	*Not rated*	*Not rated*	Fair
Verster 2008	*Not rated*	*Not rated*	Fair

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Weisler 2006	Method NR	Yes	No; placebo group had significantly lower previous use of stimulants Also - Figure 2 (baseline characteristics) for the 'ITT' population only	Yes	NR	NR	Yes
Wender 1981	Method NR	Method NR	NR	Yes	Yes but method not described	NR	Yes but method not described
Wender 1985	Method NR	Method NR	NR by phase; same subjects exposed to both treatments	Yes	Yes	NR	Yes
Wernicke 2004	Method NR	Method NR	NR	Yes	Yes	NR	Yes but method not described
Wigal 2011	Probably; "fixed-block randomization schedule)	Unclear	Unclear; no comparison of characteristics based on order of randomization to crossover design	Yes	Unclear; described as double-blind, but use of open-label dose optimization phase may have increased risk of detecting drug assignment	Unclear; described as double-blind, but use of open-label dose optimization phase may have increased risk of detecting drug assignment	Unclear; described as double-blind, but use of open-label dose optimization phase may have increased risk of detecting drug assignment
Wilens 1999	Method NR	Method NR	NR by phase; same subjects exposed to both treatments	Yes	Yes	Yes	Yes

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Intent-to-treat analysis; If No: % analyzed	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*
Weisler 2006	No 183/255 (72%) analyzed	No	*Not rated*	No/No	Yes NR NR NR
Wender 1981	Unclear	No	*Not rated*	No/No	NR NR NR NR
Wender 1985	No	No	*Not rated*	No/No	Yes NR NR NR
Wernicke 2004	No: 99.2%	No	*Not rated*	No/No	Attrition yes
Wigal 2011	No, excluded 15%	*Not rated*	Unclear	*Not rated*	*Not rated*
Wilens 1999	Yes	No	*Not rated*	No/No	Yes NR NR NR

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? (*Update 4*)	Quality rating
Weisler 2006	*Not rated*	*Not rated*	Poor
Wender 1981	*Not rated*	*Not rated*	Fair
Wender 1985	*Not rated*	*Not rated*	Fair
Wernicke 2004	*Not rated*	*Not rated*	Fair
Wigal 2011	Probably for all; protocol nonadherence/noncompliance was 0%	Yes, Yes	
Wilens 1999	*Not rated*	*Not rated*	Fair

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Wilens 2001	Method NR	Method NR	Yes	Yes	Yes	NR	Yes
Winhusen 2010	Yes, "completed by computer"	Yes, "…at a central location"	Yes	Yes	Yes for patient-assessed primary outcome; unclear for secondary outcomes rated by others	Yes, matching placebo	Yes, matching placebo
Wood 1976	Method NR	Method NR	Same 11 subjects in both drug groups	Yes	NR	NR	Yes but method not described

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Intent-to-treat analysis; If No: % analyzed	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*
Wilens 2001	Yes	No	*Not rated*	No/No	Yes NR NR NR
Winhusen 2010	Yes	*Not rated*	Yes	*Not rated*	*Not rated*
Wood 1976	Yes	No	*Not rated*	No/No	Yes NR NR NR

Evidence Table 8. Quality assessment of placebo-controlled trials in adults with attention deficit hyperactivity disorder

Author, Year	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Acceptable levels of overall attrition and between-group differences in attrition? (*Update 4*)	Quality rating
Wilens 2001	*Not rated*	*Not rated*	Fair
Winhusen 2010	Unclear, Yes, Unclear	Yes, Yes	Good
Wood 1976	*Not rated*	*Not rated*	Fair

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Adler 2005 U.S./Canada	Interim analysis of open-label extension study Setting: multicenter, 31 sites	Atomoxetine, maximum total daily dose did not exceed 160 mg/day (mean final dose=98.6 mg/day, median final dose=120 mg/day) Duration: 97 weeks	Individuals at 31 sites in U.S. and Canada; time frame NR	385
Barbaresi 2007 (Fair)	Retrospective, population-based cohort	Any stimulants Duration: Followed from age 5 until emigration, death, school graduation, or dropout. Median age at last follow-up was 18.4 years	Cumulative school records for every child born in Rochester, MN between January 1, 1976 and December 31, 1982 to mothers residing in Independent School District	370
Batterson 2005 (Poor)	Cross-sectional study	MPH IR at a minimum dose of 20 mg/day Duration: N/A	Children who had taken MPH for a minimum of 2 years at the time of exposure of a panoramic radiograph. Time frame NR.	84

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Adler 2005 U.S./Canada	Mean age=42.4 years 64.1% male 92.2% White 3.6 % Hispanic 2.1 % African American 1.0% Eastern Asian 0.5% Western Asian 0.5% other	NR
Barbaresi 2007 (Fair)	Median age at last follow-up: 18.4 years 74.9% male Ethnicity NR	**Academic achievement** Stimulant yes/no: P = 0.75 Average daily dose: P = .058 Duration of treatment with stimulants, yr: P= 0.32 Age at onset of treatment with stimulants, yr: P = 0 .66 Type of educational intervention: P < 0.001 Maternal education at birth: P < 0.001 **Percentage of days absent by grade level** Stimulant yes/no: P=0.012 Average daily dose: P=0.71 Duration of treatment with stimulants, yr: P=0.041 Age at onset of treatment with stimulants, yr: P=0.34 Comorbid conditions: P=0.006 Type of educational intervention: P<0.001 Maternal education at birth: P=0.005 **Grade retention** Type of educational intervention: P<0.001 Maternal education at birth: P<0.001 **Dropping out of school** Stimulant yes/no: P=0.54 Average daily dose: P=0.35 Duration of treatment with stimulants, yr: P=0.52 Age at onset of treatment with stimulants, yr: P=0.54 Comorbid conditions: P=0.003 Type of educational intervention: P<0.001 Maternal education at birth: p<0.001
Batterson 2005 (Poor)	Mean age: 11.6 years 71% male Race NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Adler 2005 U.S./Canada	Mean decrease in weight of 1.3 kg, p<.001 Increases in heart rate, mean change 5.1 bpm, p<.001 Increases in blood pressure, mean change for systolic and diastolic <2.0 mm Hg, p<.05 No clinically relevant changes in QTc (Fridericia) No clinically significant changes in lab measures	Eli Lilly and Co.	35 (9.1%) of patients rolled into the open-label trial w/out entering the discontinuation period of the previous studies
Barbaresi 2007 (Fair)	NR	Public Health Service, National Institutes of Health (HD29745 and AR30582) and McNeil Consumer and Specialty Pharmaceuticals	
Batterson 2005 (Poor)	MPH IR vs control Dental age (years): 12.20 vs 12.58, NS	NR	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Brehaut 2003 Canada (Fair)	Population-based database analysis	MPH (mean dose NR) Duration: NR	British Columbia Linked Health Dataset (BCLHD) January 1, 1990 and December 31, 1996	1,026,873
Charach 2006 (Poor)	Open-label extension study	Psychostimulants (% patients): 43 (54%) DEX: 19% MPH: 81% Dosages NR Duration: 5 years	Children who had completed a 12-month randomized-controlled trial of combined MPH and parent-treatment groups; original trial began in 1993	79

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Brehaut 2003 Canada (Fair)	Male, without childhood behavior disorders: 50.9% Male, with childhood behavior disorders: 81.6%	NR
Charach 2006 (Poor)	NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Brehaut 2003 Canada (Fair)		British Columbia Health Research Foundation (212-95-1), and the Sunny Hill Foundation for Children	

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

Charach 2006 (Poor)	Association between increased dose and height (controlled for time since initiation of treatment): ß coefficient = -0.11, p<0.001 Association between increased dose and weight (controlled for time since initiation of treatment): ß coefficient = -0.29, p<0.001	National Health Research Development Program of Canada, and the Department of Psychiatry of the Hospital for Sick Children, Toronto, Ontario, Canada	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Charles 1981 (Fair/Poor)	Cross-sectional	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) Duration: 4 years	Setting: UCLA Department of Pediatrics	62
Donner 2007 (Poor)	Open-label, non-comparative, community-based study	Once daily dose of MAS XR of 10, 20 or 30 mg/d according to medication-conversion algorithm Mean dose NR Duration: Initial treatment: 7 wks Extension treatment: initial treatment and 4 wks + 3 days more	Participants recruited using direct clinic referrals. Time frame NR.	2280 for initial phase, 441 for extension phase
Faraone 2005 U.S. (Poor)	Open-label extension study Setting: multicenter	MAS XR 10-30 mg/day (mean dose NR) Duration: 6-30 months	Children from two separate acute studies: (1) a randomized, double-blind, placebo- and active-controlled, crossover study of MAS-XR, and (2) a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of MAS-XR. Time frame NR.	568

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Charles 1981 (Fair/Poor)	Mean age=12 years, 3 months 79% male 88.7% white 9.7% black 1.6% Hispanic	Group 1 vs 2 vs 3 vs 4 vs 5 Teacher reports of below grade level work (% children): Reading: 77 vs 75 vs 64 vs 73 vs 83 Spelling: 69 vs 75 vs 64 vs 55 vs 75 Mathematics: 69 vs 100 vs 56 vs 73 vs 58 Ability to sustain attention: 38 vs 75 vs 71 vs 73 vs 75 Unclear oral language: 15 vs 12 vs 14 vs 45 vs 50 Other Percentage of repeated grades (%): 46 vs 50 vs 36 vs 31 vs 8 Special education class placement: 31 vs 60 vs 36 vs 31 vs 58 Currently tutored: 15 vs 30 vs 14 vs 23 vs 41
Donner 2007 (Poor)	Average age: 9.5 yrs ± 1.8 Male: 76.1% White: 88% African American: 6.7% Asian/Pacific Islander: 0.3% Hispanic: 3.5% Native American: 0.1% Other: 1.4%	NR
Faraone 2005 U.S. (Poor)	Mean age 8.7 years (6-12) 78% male 73% White 12% Black 9% Hispanic 19% Asian/Pacific Islander 3% other	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Charles 1981 (Fair/Poor)	NR		
Donner 2007 (Poor)	<u>MAS XR 10mg/d vs MAS XR 20 mg/d vs MAS XR 30 mg/d vs MAS XR 40 mg/d</u> Mean SBP(mm Hg) change from baseline to final visit: 0.4 vs 1 vs 0.2 vs 0.7 Mean DBP (mm Hg) change from baseline to final visit: 0.5 vs 0.8 vs 0.6 vs 0.5 Pulse (bpm) from baseline to final visit: 1.2 vs 1.6 vs 1.8 vs 1.3 <u>New abnormalities (total pts)</u> Atrial premature complex: 2 Ventricular premature complex: 6 Incomplete right bundle-branch block: 6 Increased QT interval: 2 Left anterior hemi-block: 9 Right bundle-branch block: 5 Low voltage morphology: 2 Right ventricular hypertrophy morphology: 1 Ectopic atrial rhythm: 27 Sinus tachycardia: 2 T-wave: 9 U-wave abnormality: 1	Shire Pharmaceuticals	
Faraone 2005 U.S. (Poor)	Growth was less than expected based on CDC norms Losses in expected weight and BMI were greatest for heaviest children, losses in expected height were greatest for tallest children Nearly all growth deficits occurred in year one; loss in expected growth NS in year 2 Those previously treated with stimulants showed smaller weight and height deficits for the first year	Shire Pharmaceutical Development	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Findling 2005 U.S. (Poor)	Open-label extension study Setting: multicenter	MAS XR; Adderall XR® (mean dose ranged from 20 mg/day at 3 months to 22 mg/day at 24 months) Duration: 2 years	Subjects previously enrolled in 1 of 2 double-blind, placebo-controlled MAS XR studies.	568
Forrester 2006 (Poor)	Cross-sectional study	MPH IR dosage NR Annual	Cases were all calls involving MPH IR received during 1998-2004. Data source: Texas Poison Control Network (TPCN)	322

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Findling 2005 U.S. (Poor)	Mean age 8.7 years (6-12) 78% male 73% White 12% Black 9% Hispanic 4% other	NR
Forrester 2006 (Poor)	Age (years): < 13: 20.3% 13-19: 54.7% > 19: 25% 61.9% male Race NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Findling 2005 U.S. (Poor)	4 (0.7%) cardiovascular AEs: 1 (0.2%) tachycardia (108 bpm at baseline, 101 to 121 bpm long-term treatment), moderate in severity, MAS XR 20 mg/day 2 (0.4%) intermittent chest pain that resolved, mild in severity, MAS XR 20 mg/day (1 at 9 months, 1 at 12 months) 1 (0.2%) hypertension, 130/90 mm Hg after 12 months, moderate severity, MAS XR 10 mg/day Change in group mean QT interval corrected by Bazett's formula (QTcB) values NS Most common ECG abnormalities, none clinically significant, at MAS XR 20 mg/day, were: 25 (4.4%) sinus arrhythmia 5 (0.9%) ST-T wave abnormalities 4 (0.7%) poor anterior R-wave progression	Shire Pharmaceutical Development	
Forrester 2006 (Poor)	Medical outcomes: All MPH IR exposures vs MPH IR abuse exposures vs MPH IR nonabuse exposures: No effect: 49.9% vs 28.6% vs 52.1% Minor effect: 28.5% vs 36.5% vs 27.7% Moderate effect: 19.2% vs 29.1% vs 18.2% Major effect: 2.4% vs 5.8% vs 2.0% Death: 0 vs 0 vs 0 Proportion of annual human abuse calls relating to MPH IR: 1998: 10.6% 1999: 11.4% 2000: 7.2% 2001: 5.9% 2002: 7.4% 2003: 9.8% 2004: 7.3% Total: 8.5%	Commission on State Emergency Communications in Texas	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Gadow 1999 U.S. (Fair)	Long-term follow-up to participation in an 8-week controlled trial of MPH and placebo Non-comparative	MPH 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 Duration: 2 years	Children who had participated in an 8-week, double-blind, placebo-controlled MPH evaluation. Time frame NR.	34
Garnier 2010 U.S. (Poor)	Cross sectional	Amphetamine/DEX, MPH, MPH extended release, other; dosages not reported Duration: Not reported, "current use"	Time Frame: August 2006 to August 2007 Data source: Survey of college students from a large public university in the mid-Atlantic region of the United States. Data from third annual interview of cohort participating in prospective, longitudinal study of health behaviors	Overall=483 Prescribed ADHD medication=81 Amphetamine or DEX=44 MPH=27 MPH extended release=23 Other=11

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Gadow 1999 U.S. (Fair)	Short-term dose trial (n=34) Mean age=8.8 91.2% male Race NR	NR
Garnier 2010 U.S. (Poor)	Overall: 46% male 77% white Mean age not reported (range, 17 to 19 years) 46% met criteria for alcohol use disorder in past year 19.7% ever diagnosed with ADHD Characteristics for subgroup prescribed ADHD medication not reported	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	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) Yale Global Tic Severity Scale: 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 Shapiro Tourette Syndrome Severity Scale: 2.9/1.6/1.8/2.0/1.9/1.9 Tourette Syndrome Clinical Global Impression Scale: 2.6/3.1/3.1/2.3/2.4/2.3 Tourette Syndrome 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 Global Tic Rating Scale 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-Obsessive Compulsive-Disorder: 2.7/1.6/1.8/1.7/1.9/1.8 Parent Ratings Global Tic Rating Scale 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	Tourette Syndrome Association Inc., and the Public Health Service (grant MH45358) from the National Institute of Mental Health	Only 2 comparisons indicated that tics were worse on medication than placebo (data NR)
Garnier 2010 U.S. (Poor)	Individuals who diverted medication: Amphetamine or DEX=70.5% MPH=37.0% MPH extended release=39.1% Other=27.3% For overall group, multivariate analyses found 'number of prescription drugs used nonmedically in the past year' and 'childhood conduct problems' to be significantly associated with diversion, independent of demographics and other risk factors. Correlates of diversion not investigated for ADHD drug subgroup.	National Institute on Drug Abuse, National Institutes of Health and an investigator-initiated award from Ortho-McNeil-Janssen	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Gau 2006 (Fair)	Cross sectional	MPH IR BID or TID or QID Duration: NR	Patients from two medical centers (outpatient clinic of the Department of Child Psychiatry of National Medical Center in north Taiwan, and a private medical center in south Taiwan), and the ADHD Educational Foundation in Taiwan. Time frame NR.	307
Goldman 2008 U.S. (Fair/Poor)	Case control	MPH DEX Combined DEX and amphetamine Duration: 5 years	All patients with symptoms of cold hands and feet seen at the rheumatology clinic of Akron Children's Hospital and Medical Center between January 2001 and December 2005 underwent pulse volume recording with ice water exposure at a vascular laboratory. The charts of these patients were reviewed for the present study.	64

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Gau 2006 (Fair)	Mean (SD) age: 10.7 (2.7) years Male: 88.3% Ethnicity: Asian 100%	Poor adherents: 25.7%, good adherents: 74.3% Age (increment by 1 year)and its correlation to adherence: OR 1.24, CI 1.10-1.39, p<0.001 Gender (male vs female): OR 1.77, CI 0.60-5.43 Dosing Frequency and its correlation to Adherence: BID vs. QD: OR 2.12, CI 0.93-4.83 TID vs QD: OR 2.58, CI 1.10-6.08, p<0.05 QID vs QD: OR 2.28, CI 0.23-22.64 Scale sores: mean(SD) good adherence vs bad adherence Chinese Health Questionnaire score: 1.95 (2.23) vs 3.62 (3.17),p<0.0001 Family Adaptation, Partnership, Growth, Affection, Resolve score: 7.98 (2.65) vs 9.16 (3.25), p<0.01 Parenting style by Parental Bonding Instrument: Affection care: 26.15 (4.68) vs 24.61(5.11), p<0.05 Protection: 14.34 (4.59) vs 16.33 (4.91), p<0.01 Social Adjustment Inventory for Children and Adolescents score: Interaction with mother: 1.68 (0.55) vs 1.93 (0.70), p<0.01 Interaction with father: 1.92 (0.64) vs 2.16 (0.78), p<0.05 Problems with parents: 1.54 (0.53) vs 1.76(0.61), p<0.01
Goldman 2008 U.S. (Fair/Poor)	Mean age cases: 15.9 years controls: 16.1 years 28.2% males Ethnicity: NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Gau 2006 (Fair)	NR	National Taiwan University Hospital, and the National Science Council	
Goldman 2008 U.S. (Fair/Poor)	McNemar's test showed a significant association between past or current use of ADHD stimulants and the presence of RS (x^2=5.00, P=0.01) Controls had significantly higher CRP levels compared to cases (P=0.03) Controls had significantly higher ESR levels compared to cases (P<0.001)	NR	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
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. Comparative	MPH mean dose 34 mg/day, n=60 DEX mean dose 16.5 mg/day, n=24 (Imipramine/desipramine, n=16) Subjects received at least 2 (mean=5) years of treatment. Mean follow-up time: 5.8 years for MPH, 6.8 years for DEX.	All the weight and height data the researchers were able to accumulate from past records of children they had been treating, as well as measurements made in their office. Time frame NR.	100
Gualtieri 1985 U.S. (Fair)	Open-label 3-6 month follow-up of MPH responders	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. Duration: 3-6 months		8

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Gross 1976 U.S. (Fair)	Mean age at onset of treatment: 9 Gender 82% Ethnicity NR At final measurement, 45% were aged 16+ 17% were aged 18+	NR
Gualtieri 1985 U.S. (Fair)	Mean age 27.2 100% male Ethnicity NR (represents n=22, of which 8 were included in the long-term followup study)	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Gross 1976 U.S. (Fair)	Average in percentile of weight, MPH vs DEX: Time after onset: 1 year, -5.2 (p<0.05) vs -5.9 (NS); 2 year, -4.3 (NS) vs -6.0 (NS); 3 year: -3.0 (NS) vs -3.4 (NS)	NR	Loss of weight compared with expected norms occurs during the first 3 years with MPH and DEX, 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.

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.

Gualtieri 1985 U.S. (Fair)	One subject consumed a month's supply of MPH in "an abortive suicide attempt".		

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Hechtman 1984 (Fair)	Retrospective cohort study	MPH 20-50mg/day Duration: 3 years between 6-12 years of age	Hyperactive children first referred to the child psychiatry clinic between 6 and 12 years of age for sustained hyperactivity both at home and at school	104
Holick 2009 (Fair)	Retrospective cohort	Atomoxetine or stimulant ADHD medication with daily dosage values up to 240 mg Duration: Mean exposure during follow-up not reported, but mean follow-up was 1.5 years	Time Frame: January 1, 2003 through December 31, 2006 Data source: Automated medical and pharmacy claims from the Ingenix Research DataMart	Stimulant ADHD medication=21,606 Atomoxetine=21,606
Horrigan 2000 U.S. (Fair)	Before-after, retrospective	Adderall (modal dose 10 mg bid) Duration: 12 months	Outpatients diagnosed and treated with Adderall during a 12-month period at a university-based neuropsychiatric clinic. Time frame NR.	24

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Hechtman 1984 (Fair)	Mean age=21.8 years Gender: NR Ethnicity: NR	Stimulant-treated hyperactives (STH), non-STH, Matched controls (MC): Demographic data: residential moves: STH>MC, p<0.05 live with girlfriends/wives: STH>MC, p<0.02; STH>non-STH, p<0.01 future vocational 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 earlier: 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
Holick 2009 (Fair)	After propensity score matching: 52% male 26% age 18-24 years 10% age 25-29 years 24% age 30-39 years 25% age 40-49 years 15% age 50-64 years 1% age ≥ 65 years 45% ADHD 10% hypertension 1% smoking	NR
Horrigan 2000 U.S. (Fair)	Mean age=33 50% male Ethnicity NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Hechtman 1984 (Fair)	NR	National Institute of Mental Health	
Holick 2009 (Fair)	Current use, as-treated analyses: atomoxetine versus stimulant ADHD medication; IR=incidence rate per 1000 person-years; RR=crude relative risk (covariate-adjusted models unable to converge due to small number of cases) CVA: IR=0.52 versus 0.38; RR 1.38 (95% CI 0.42 to 4.54) TIA: IR=0.10 versus 0.33; RR 0.31 (95% CI 0.04 to 2.63) As-matched analysis: atomoxetine versus stimulant ADHD medication; HR=hazard ratio adjusted for calendar year CVA: IR=0.32 versus 0.35; HR 0.91 (95% CI 0.39 to 2.16) TIA: IR=0.22 versus 0.29; HR 0.78 (95% CI 0.29 to 2.08)	Contract between i3 Drug Safety, a division of Ingenix Pharmaceutical Services and Eli Lilly and Company	
Horrigan 2000 U.S. (Fair)	Motor tic: 1/24 (4%)	NR	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Kemner 2006 (Fair)	Retrospective cohort	MPH IR 30 mg vs MPH ER 36 mg Duration: 12 months	Data source: Integrated Health Care Information Services National Managed Care Benchmark Database Data collection period: 2/1/00-12/31/02	5939
Kemner 2006b (OROS MPH vs. TID IR MPH) (Fair)	Retrospective cohort	TID IR MPH: dose not reported OROS MPH: dose not reported 81% of the sample initiated therapy on OROS MPH Duration: 12 months	Data source: Integrated Health Care Information Services National Managed Care Benchmark Database Data collection period: 2/1/00-12/31/02	5939
Kratochvil 2001 U.S. (Fair)	Before-after, prospective	Tomoxetine mean dose NR Duration: 10 weeks	Setting: 1 of 24 clinical research sites involved in an ongoing multicenter study. Time frame NR.	100

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Kemner 2006 (Fair)	Mean age=15 years 77% male Race NR	NR
Kemner 2006b (OROS MPH vs. TID IR MPH) (Fair)	Mean age=15 77% male Race NR	OROS MPH vs. TID IR MPH 15 day Gap in ITT medication: 85% vs. 97%, P<0.0001 30 day Gap in ITT medication: 77% vs. 95%, P<0.0001 Switch to another ADHD med: 27% vs. 68%, P<0.0001 Switch to other ITT med: 1% vs. 33%, P<0.0001 Days on ITT medication: 90% compliant: 24% vs. 5%, P<0.0001 80% compliant: 29% vs. 7%, P<0.0001 75% compliant: 30% vs. 5%, P<0.0001 Hospitalizations -- OROS MPH : OR=0.668, P=0.045 (Individuals who received OROS MPH were 33% less likely to be hospitalized compared to individuals who received TID IR MPH)
Kratochvil 2001 U.S. (Fair)	Mean age NR 100% male 90% White 10% Hispanic	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Kemner 2006 (Fair)	Table 2. **Factors Affecting Emergency Room Visits and the Number of Visits** See table below	NR	
Kemner 2006b (OROS MPH vs. TID IR MPH) (Fair)	NR	McNeil Consumer and Specialty Pharmaceuticals	
Kratochvil 2001 U.S. (Fair)	Weight change (mean change): -0.15 kg, p=NS	Lilly Research Laboratories	

Variable	Probability of an Emergency Room Visit: Odds Ratio (95% CI)[a]	p	No. Emergency Room Visits: Point Estimate (95% CI)	p
Age	1.00 (0.99 to 1.01)	NS	–1.98 (–0.01 to 0.01)	NS
Female	1.01 (0.89 to 1.20)	NS	0.00 (–0.13 to 0.17)	NS
Geographic region				
East	1.90 (1.46 to 2.41)	<0.0001	0.00 (0.80 to 1.25)	<0.0001
South	1.40 (0.86 to 2.29)	NS	1.02 (0.43 to 1.29)	<0.0001
North Central	2.50 (1.39 to 4.48)	0.002	0.86 (0.56 to 1.67)	<0.0001
West	0.99 (0.68 to 1.45)	NS	1.11 (0.69 to 1.31)	<0.0001
HMO insurance	1.04 (0.89 to 1.21)	NS	1.00 (–0.07 to 0.20)	NS
Total no. diagnoses preinitiation	1.05 (1.03 to 1.08)	<0.0001	0.05 (0.03 to 0.07)	<0.0001
Diagnosis associated with ADHD				
Anxiety	1.09 (0.53 to 2.24)	NS	–0.12 (–0.78 to 0.54)	NS
Depression	0.93 (0.48 to 1.79)	NS	–0.25 (–0.84 to 0.35)	NS
Oppositional disorder	1.31 (0.095 to 1.81)	NS	0.29 (0.00 to 0.59)	0.05
Drug or alcohol abuse	2.59 (1.61 to 4.17)	<0.0001	0.88 (0.46 to 1.30)	<0.0001
Accident or injury	37.97 (28.16 to 51.20)	<0.0001	1.95 (1.75 to 2.14)	<0.0001
ER methylphenidate	0.79 (0.60 to 0.95)	0.01	–0.21 (–0.37 to 0.05)	0.01

[a]CI = confidence interval, NS = not significant, HMO = health maintenance organization, ADHD = attention-deficit/hyperactivity disorder.

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Lage 2004 (Fair)	Retrospective cohort	XR MPH TID IR MPH Duration: NR	Data resource: Integrated Health Care information Services (IHCIS) National Managed Care Benchmark Database, December 18, 1999–August 14, 2002.	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Lage 2004 (Fair)	Mean age=9.73 years 75% male Ethnicity: NR	Treatment pattern- XR MPH vs TID IR MPH, p value Days supplied: 186 vs 127, p<0.0001 Discontinue, stopped receiving all ADHD medications prior to t+1 year-28days: 47% vs 72%, p<0.0001 Switch, stopped prescription for one ADHD medication and started prescription 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

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Lage 2004 (Fair)	NR	Janssen-Ortho Inc.	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Lerer 1977 (Fair)	Before-After	MPH mean=43mg/day Range=40-60mg/day Duration: 60 days - 6 months	Patients referred to the senior author for a variety of behavioral and academic difficulties. Time frame NR.	27
Marcus 2005 (Fair)	Retrospective cohort	ER-MPH IR-MPH Duration: 12 months	Statewide California Medicaid claims files, January 1, 2000-December 31, 2003	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Lerer 1977 (Fair)	Mean age=15.5 years Gender: 92.6% male Ethnicity: 100% white	15 (55.6%) have shown impressive gains in behavior control 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.
Marcus 2005 (Fair)	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	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 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Lerer 1977 (Fair)	NR	NR	
Marcus 2005 (Fair)	NR	McNeil Consumer & Specialty Pharmaceuticals	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Mattes 1983 U.S. (Fair)	Before-After (open trial of MPH) Non-comparative	MPH mean dosages (mg): Up to 1 year: 39.9 1-2 year: 41.3 2-3 year: 41.0 3-4 year: 41.4 Duration: 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	NR	86

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Mattes 1983 U.S. (Fair)	NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Mattes 1983 U.S. (Fair)	See below	Public Health Service grants	Once a year the MPH 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; MPH therapy was reinstated in the fall only if behavioral complaints from school were received.

Year	N	Pretreatment	End of year	t	p	Correlation with treatment duration (Pearson's r, p-value)	Correlation with mean daily dose (Pearson's r, p-value)	Correlation with total cumulative dose (Pearson's r, p-value)
Height								
1	51	51.1	49.7	1.56	NS	-.20, NS	0.04, NS	-0.17, NS
2	56	51.7	43.6	7.10	<0.001	0.18, NS	0.09, NS	0.16, NS
3	37	60.5	47.1	8.13	<0.001	0.04, NS	0.29, NS	0.24, NS
4	19	66.6	48.5	6.50	<0.001	0.33, NS	0.15, NS	0.28, NS
Weight								
1	69	59.2	49.5	6.81	<0.001	0.17, NS	0.17, NS	0.26, p<0.05
2	69	57.4	41.5	9.24	<0.001	0.31, p<0.01	0.12, NS	0.29, p<0.05
3	44	62.1	43.5	10.18	<0.001	0.05, NS	0.05, NS	0.09, NS
4	26	62.5	41.9	5.82	<0.001	0.39, p<0.05	-0.01, NS	0.018, NS

Multiple regression analysis of relationship of dosage and final height (n=42, includes 6 children who were off MPH at 3 years)

Step	Factors	Multiple correlation	Total explained variance (%)	Unique variance contribution of each factor (%)
1	Baseline height	0.94	87.8	87.8 (Pearson's r)
2	Baseline weight	0.94	88.2	0.4
3	Age at final height measurement	0.94	88.3	0.0
4	Baseline age	0.94	88.5	0.2
5	Total cumulative dosage of MPH	0.95	90.5	2.0 (p<0.01)

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
McAfee 2008 U.S. (Fair)	Retrospective cohort	Atomoxetine or other ADHD medications (stimulants and bupropion); dosage not reported Duration: Mean exposure during follow-up not reported	Time Frame: During or before 2003 Data source: Automated medical and pharmacy claims from the Ingenix Research DataMart	Atomoxetine only=982 Other ADHD medications=22,506
McCarthy 2009 UK	Retrospective cohort	Methylphenidate Dexamfetamine Atomoxetine Dose, duration of exposure not reported	UK General Practice Research Database, January 1, 1993 to June 30, 2006	N=5351 (18,637 patient-years)

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
McAfee 2008 U.S. (Fair)	74% male 59% ages 6-12 years 41% ages 13-17 years Seizure risk factors: Congenital=4%, CNS=10%, Systemic=32%, Substance=17%	NR
McCarthy 2009 UK	Patients aged 2 and 21 years with at least one prescription for methylphenidate, dexamfetamine or atomoxetine.	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
McAfee 2008 U.S. (Fair)	Incidence rate of first medical claim of seizure for current use (per 1000 person-years): Atomoxetine=5.9, other ADHD therapy=4.2 Adjusted relative risk (95% CI) of first medical claim of seizure for current use versus nonuse: Atomoxetine=1.1 (0.6 to 2.1); other ADHD therapy=0.8 (0.6 to 1.3); crude and adjusted nested case control analyses did not differ in any meaningful was from the cohort analysis results Seizure risk factors in overall group: Demographics (versus males, age 13-17): Female age 6-12=1.7 (0.9 to 3.3), Female age 13-17=1.4 (0.7 to 3.0), Male age 6-12=1.6 (1.0 to 2.7) Seizure risk factors: Congenital versus no congenital=1.2 (0.5 to 2.4); CNS versus no CNS=4.6 (3.0 to 7.0); systemic versus no systemic=1.1 (0.7 to 1.6); substance versus no substance=1.8 (1.2 to 2.8)	Contract between i3 Drug Safety, a division of Ingenix Pharmaceutical Services and Eli Lilly and Company	
McCarthy 2009 UK	7 deaths total; crude mortality rate 37.6 [per 100,000 patient-years. SMR (calculated indirectly): 1.44 (95% CI 0.58, 2.96) No sudden deaths in 6 patients with a confirmed cause of death. Suicide in 2 patients, overdose of unknown intent in 1 patient. SMR for suicide for children aged 11-14 years 161.91 (95% CI 19.61, 584.88) SMR for suicide for children aged 15-21 years 1.84 (95% CI 0.05, 10.25)	License for the General Practice Research Database funded by the European Commission via the Taskforce European Drug Development for the Young (TEDDY) network of Excellence European Commission Framework 6 Programme 2005-2010. No specific funding was obtained for the conduct of this study.	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
McGough 2005 U.S. (Fair)	Multicenter Long-term follow-up of two different placebo-controlled trials of Adderall	Adderall XR (MAS) Starting dose was 10 mg/d and could be up titrated by 10 mg increments to 20 or 30 mg/d. Duration: 24 months	Subjects previously enrolled in one of two double-blind, placebo-controlled MAS XR studies (Biederman 2002 and McCracken 2003). Time frame NR.	568
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 MPH	MPH mean daily doses: 12-month cohort: 24.1 mg 24-month cohort: 29.1 mg Dosing schedule NR Duration: ≥ 8 months of medication during a 12-month period ≥ 16 months of medication during a 24-month period	Setting: Physical Fitness Research Laboratory at Institute for Child Behavior and Development, University of Illinois at Urbana-Champaign	NR
Miller-Horn 2008 U.S. (Fair)	Retrospective cohort (database analysis)	(i) Amphetamine/DEX extended release (Adderall XR) (ii) Amphetamine/DEX (Adderall) (iii) osmotic controlled-released formulation of MPH (OROS) (iv) atomoxetine (Strattera) (v) MPH standard release (MPH) Duration: 24 months	Children treated for ADHD at St. Christopher's Hospital for Children (Philadelphia, PA) neurology clinic over a 24-month period from 2002 to 2004, identified by a retrospective database analysis	137

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
McGough 2005 U.S. (Fair)	Mean age: 8.7 years 78% male 73% white 12% Black 9% Hispanic 1% Asian/ Pacific Islander 3% Other	NR
McNutt 1976a (preliminary report)/McNutt 1976b U.S. (Fair)	Medicated (n=28) vs nonmedicated (n=24) vs control (n=47) vs overall 12-month 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 24-month 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
Miller-Horn 2008 U.S. (Fair)	Mean age males: 9.9 years females: 10.9 years 79.6% male Ethnicity: NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
McGough 2005 U.S. (Fair)	92% (n=525) of patients had ≥ 1 AE during the study. Of patients reporting AEs, 84% (n=440) experienced at least 1 AE deemed by the investigator to be "possibly" treatment related. Most frequently reported AEs: headache (15% of all AEs), anorexia (15% of all AEs), and insomnia (11% of all AEs). 21 serious AEs (Serious AEs) were reported by 18 patients (3%); only 2 (both convulsions) were thought to be related to Adderall; both were discontinued from the study. 12 Serious AEs were severe, but none were thought to be related to Adderall. 84 patients (15%) withdrew due to AEs; the most frequently reported AEs associated with treatment withdrawal included weight loss (n=27), anorexia/decreased appetite (n=22), insomnia (n=11), depression (n=7), and emotional lability (n=4). Overall medication compliance was 94%. Mean systolic blood pressure increased by 3.5 mmHg, diastolic blood pressure increased by 2.6 mmHg, and mean pulse increased by 3.4 beats/min. 134 reports of weight loss occurred over the 24 months. The decrease in the expected weight gain was -7.8 kg for the patients above the 75th percentile on the CDC weight charts at baseline, and was -2.1kg for patients below the 25th percentile at baseline.	Shire Pharmaceutical Development Inc.	635 patients were enrolled in the original PCTs; 568 enrolled from those studies into this long-term extension.
McNutt 1976a (preliminary report)/McNutt 1976b U.S. (Fair)	<u>12 months</u> 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 <u>24 months</u> 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
Miller-Horn 2008 U.S. (Fair)	35 of 137 reported side effects (25%) Adderall XR vs Adderall vs OROS vs Strattera vs MPH Insomnia: 3.8% vs 22.2% vs 12.5% vs 6.7% vs 8.7% Tics: 0% vs 5.5% vs 2.5% vs 3.3% vs 8.7% Decreased appetite: 15.4% vs 22.2% vs 17.5% vs 10% vs 8.7% Headaches: 11.5% vs 11.3% vs 10% 0% vs 4.3% (P=0.035)	NR	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Millichap 1977 U.S. (Fair)	Before-After	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 Duration: 6-26 months (mean=16 months)	Patients referred for pediatric neurology evaluation because of hyperactive behavior and failure to achieve the level of academic potential expected	36
Olfson 2007 (Fair)	Retrospective, claims data review	ER-MPH IR-MPH Duration: 4 year period of claims data	Pharmacy and medical claims for 75 US managed care plans representing approximately 55 million beneficiaries for dates of service from January 1, 2000 through December 31, 2004	5,122
Paternite 1999 (Fair)	Descriptive study	MPH mean=32mg/day Range=8-80mg/day Duration: Mean=30.4 months, range=1-76 months	Patients with diagnoses of hyperkinetic reaction or a minimal brain dysfunction syndrome were treated with MPH at the University of Iowa outpatient child psychiatry clinic between 1967-1972	97
Pliszka 2006 (Poor)	Retrospective cohort	MPH (any form) vs MAS (any form) Highest daily dosages: 34.8 mg vs 22.7 mg Mean duration: 2.6 years	University-based child and adolescent psychiatry/psychopharmacology clinical database	179

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Millichap 1977 U.S. (Fair)	Mean age NR 100% male Race NR	NR
Olfson 2007 (Fair)	ER-MPH Mean age: 31.2 years 60.3% male Ethnicity NR IR-MPH Mean age: 33.3 years 55.8% male Ethnicity NR	ER-MPH vs IR-MPH Overall median days on treatment: 68.0 vs 39.0 2 or more stimulant pharmacy claims: 61.4% vs 50.5% (p<0.001) Median days on treatment for those with 2 ore more stimulant pharmacy claims: 138 vs 121
Paternite 1999 (Fair)	Mean age=8.8 years Gender: 100% male Ethnicity: NR	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
Pliszka 2006 (Poor)	Mean age=8.7 years 81.0% male Race NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
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%)	NR	
Olfson 2007 (Fair)	NR	Ortho-McNeil Janssen Scientific Affairs	
Paternite 1999 (Fair)	NR	National Institute of Mental Health	
Pliszka 2006 (Poor)	Final Z scores for MAS vs MPH: Height: 0.0 vs -0.2 Weight: 0.4 vs 0.6 BMI: 20.1 vs 20.9 No main effects for either stimulant type on height, weight or BMI	NR	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Quinn 1975 U.S. (Fair)	Unblinded follow-up of samples that continued their original randomly assigned medication (6-week, randomized, DB study: Rapoport, 1974) Non-comparative	MPH mean daily dose of 20.56 mg Imipramine mean daily dose of 65.4 mg Duration: 1 year	Patients at the Hyperactivity Clinic. Time frame NR.	75
Rabiner 2009 US	Survey	ADHD medication. Drug, dose, duration not specified.	Web-based survey conducted in Spring 2007	115
Rao 1998 U.S./Canada (Fair)	Retrospective cohort	MPH or pemoline Mean dosages NR Duration NR	National Cooperative Growth Study (NCGS) Database. Time frame NR.	3897

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Quinn 1975 U.S. (Fair)	Mean age NR 100% male Race NR	NR
Rabiner 2009 US	College students at two universities with a prescription for ADHD medication; 68.7% female	NR
Rao 1998 U.S./Canada (Fair)	Mean age=9.3 years 74.8% male Race NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	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 (MPH n=23; imipramine n=13) Anorexia: 9 (47%) vs 5 (39%) Seizures: none reported Condition 1=Imipramine Condition 2=MPH all doses (n=23) Condition 3=MPH > 20 mg a day (n=5) Condition 4=MPH 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	National Institute of Mental Health	
Rabiner 2009 US	31% reported having taken their medicine more often than prescribed, at a higher dose than prescribed, or using someone else's medication since beginning college. 8% reported snorting their medication during the past 6 months 1 student reported injecting medication in the past 6 months 56% were approached by a peer to give or sell them their medication in the past 6 months. 25% reported giving or selling their medication to a peer in the past 6 months. Students who had misused their ADHD medication were more likely to divert their medication than those who had not (59% vs 22%; P<0.001).	NIDA Grant R21-DA018754	
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 R2= 0.002; p=0.001	NR	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Safer 1972 U.S. (Fair)	Retrospective analysis of height and weight data Comparative	Group 1: MPH 28.7 mg/day DEX 11.8 mg/day Group 2: MPH continuous treatment for 2+ years (dose not reported; 7 of 9 subjects were also in group 1 above) Control group: no medication Duration: Group 1: 1 year Group 2: 2+ years	Patients in one of the following 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.	29
Safer 1973 U.S. (Fair)	Retrospective cohort (student health records)	DEX MPH Unmedicated controls Mean dosages NR Duration: ≥ 2 years	Forms completed by school nurses in six elementary schools in Baltimore, Maryland for all hyperactive children in their school who received stimulant medication for two or more years. Time frame NR.	44 on medication, 14 unmedicated controls

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Safer 1972 U.S. (Fair)	Group 1: Mean age 9.8 Gender NR 100% white Group 2: Mean age NR Gender NR Ethnicity NR	NR
Safer 1973 U.S. (Fair)	Mean age NR 89.8% male in children on medication; 100% male in unmedicated control group 100% white	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Safer 1972 U.S. (Fair)	See table below		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.
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	NR	Initial weight/height percentile values were initially larger for DEX group

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	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.
No medication	7	+1.3	+4.0	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.
P-value, Medicated vs. Not		p<0.05	p<0.05	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Safer 1975 (Poor)	Prospective cohort study	MPH: 27 mg/day, range 10-60mg DEX 12 mg/day, range 5-20mg Duration: 1 year	Hyperactive students at one elementary school in a suburban, blue-collar, Caucasian area from 1970-1973	NR
Sanchez 2005 (Fair)	Retrospective cohort	MPH IR, MPH SR, MPH ER, MPH OROS, MAS IR, DEX IR, DEX ER Duration: 6 months	Texas Medicaid recipients aged 5-18 years with continuous paid prescription claims from June 1, 2001-May 31, 2002	9,549
Satterfield 1979 U.S. (Good)	Prospective study of weight and height in boys treated for two years with MPH Non-comparative	MPH, taken bid (morning and noon) on 5 weekdays; some patients required a third dose mid-afternoon, 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 Duration: 2 years	Subjects were all children who were referred to Gateways Hospital Hyperkinetic Children's Clinic, Los Angeles, from September 1973 through December 1974.	72

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Safer 1975 (Poor)	Mean age: 10.3 years, range 8-13 years Gender: 80% male 100% Caucasian	NR
Sanchez 2005 (Fair)	Mean age=9.93 years 75.7% male Ethnicity NR	<u>Comparisons among stimulant groups (MAS IR vs MPH IR vs MPH OROS)</u> Persistence: 0.42 vs 0.37 vs 0.50 (F=159, df=2, p<0.0001) MPR: 0.73 vs 0.69 vs 0.76 (F=32, df=2, p<0.001) 150-180 day treatment duration (% pts): 19% vs 14% vs 30% (c^2=327, df=10, p<0.00) <u>Comparisons among age groups for all drugs combined (5-9 yrs vs 10-14 yrs vs 15-18 yrs)</u> Persistence: 0.45 vs 0.41 vs 0.41 (F=21.6, df=2, p<0.001) MPR: 0.73 vs 0.73 vs 0.67 (F=11.8, df=2, p<0.001)
Satterfield 1979 U.S. (Good)	Age range 6-12, mean age NR 100% male Ethnicity NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Safer 1975 (Poor)	Compare growth rate in school year and summer Continued group (CG): growth rate of the height and weight, NS Discontinued group (DG): DEX, weight- school year<summer, p<0.005 DEX, height- school year< summer, p<0.05 MPH, weight- school year<summer, p<0.005 MPH, height- school year< summer, p<0.05	NR	
Sanchez 2005 (Fair)	NR	Unclear	
Satterfield 1979 U.S. (Good)	<table><tr><th rowspan="2">Patient group</th><th rowspan="2">N</th><th rowspan="2">Mean dosage mg/kg/day</th><th colspan="2">Growth difference in % of expected growth (p-value); mean difference</th></tr><tr><th>Weight</th><th>Height</th></tr><tr><td colspan="5">Year 1</td></tr><tr><td>Total</td><td>72</td><td>0.47</td><td>-29% (p<0.01) 0.85 kg less</td><td>-19% (p<0.001) 1.03 cm less</td></tr><tr><td>Received summer med.</td><td>31</td><td>0.627</td><td>-35% (p<0.05)</td><td>-17% (p<0.05)</td></tr><tr><td>No summer medication</td><td>41</td><td>0.37</td><td>-24.5% (p<0.05)</td><td>-19.5% (p<0.05)</td></tr><tr><td colspan="5">Year 2</td></tr><tr><td>Total</td><td>48</td><td>0.59</td><td>-10% (ns) 0.31 kg less</td><td>+8% (ns) 0.42 cm more</td></tr><tr><td>Received summer med.</td><td>24</td><td>0.81</td><td>-20% (p<0.05) 0.67 kg less</td><td>+7.5% (ns) 0.36 cm more</td></tr><tr><td>No summer medication</td><td>24</td><td>0.37</td><td>+2.5% (ns) 0.25 kg more</td><td>+10% (ns) 0.49cm more</td></tr><tr><td colspan="5">Accumulated growth: Year 1 plus Year 2</td></tr><tr><td>Total</td><td>48</td><td>0.56</td><td>-13% (ns)</td><td>+2% (ns)</td></tr><tr><td colspan="5">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.</td></tr></table>	Public Health Service	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 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Schelleman 2011 US	Retrospective cohort	Amphetamines Atomoxetine Methylphenidate Dose and duration of use not reported; analyzed those with fewer than 180 days of use and those with at least 180 days	Data from 2 US populations (i.e. a 5-state Medicaid database [1999-2003] and the 14-state HealthCore Integrated Research Database [2001-2006]) Linked Medicare data on Medicaid-Medicare dual eligible patients.	93,470 incident users of amphetamines 19,830 of atomoxetine 128,668 matched nonusers

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Schelleman 2011 US	Subjects aged 3 to 17 years who were dispensed a solid oral dosage of amphetamines, atomoxetine, or methylphenidate.	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Schelleman 2011 US	Incident users vs nonusers (Adjusted hazard ratios, 95% CI) Sudden death or ventricular arrhythmia: Methylphenidate: 2.63 (0.29, 23.69) Any ADHD medication: 1.60 (0.19, 13.60) All-cause death: Amphetamines: 0.95 (0.52, 1.71) Methylphenidate: 0.61 (0.30, 1.25) Any ADHD medication: 0.76 (0.52, 1.12) Nonaccidental death: Amphetamines: 0.41 (0.14, 1.19) Methylphenidate: 0.85 (0.31, 2.32) Any ADHD medication: 0.53 (0.29, 0.99) Nonsuicide death: Amphetamines: 0.60 (0.28, 1.29) Methylphenidate: 0.68 (0.30, 1.54) Any ADHD medication: 0.65 (0.40, 1.04) Other outcomes/drugs not estimable due to low numbers of events Prevalent users vs nonusers (Adjusted hazard ratios, 95% CI) Sudden death or ventricular arrhythmia: Methylphenidate: 1.30 (0.15, 11.14) Any ADHD medication: 1.43 (0.31, 6.61) Stroke: Any ADHD medication: 0.89 (0.11, 7.11) All-cause death: Amphetamines: 0.92 (0.48, 1.76) Methylphenidate: 0.79 (0.48, 1.29) Any ADHD medication: 0.77 (0.56, 1.07) Nonaccidental death: Amphetamines: 0.27 (0.06, 1.18) Methylphenidate: 0.64(0.29, 1.40) Any ADHD medication: 0.43 (0.24, 0.79) Nonsuicide death: Amphetamines: 0.97 (0.45, 2.11) Methylphenidate: 0.65 (0.35, 1.20) Any ADHD medication: 0.66 (0.44, 1.00) Other outcomes/drugs not estimable due to low numbers of events	Shire	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Setlik 2009 U.S. (Poor)	Retrospective cohort	Amphetamine/DEX, MPH (including D-MPH) Duration: NR	Time frame: 1998-2005 Data source: American association of poison control center's national poison data system	Unclear
Spencer 2005 U.S. (Fair)	Open-label extension study Setting: multicenter	MAS XR, flexible dosing 10-60 mg/day, most patients (>80%) received 20-40 mg/day throughout the study Duration: 6 months	Subjects participating in a 4 week, randomized, placebo-controlled trial. Time frame NR.	138
Swanson 2006 (PATS) U.S. (Fair)	Before-After, prospective Setting: multicenter	MPH, titrated doses (average 14.2 mg/day) 3 times daily, 7 days/week Duration: ~1 year	Patients in the Preschool ADHD Treatment Study (PATS). Time frame NR.	140

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Setlik 2009 U.S. (Poor)	NR	NR
Spencer 2005 U.S. (Fair)	Mean age 14.4 years (13-17) 71.0% male 71.7% White 15.2% Black 10.1% Hispanic 2.8% other	NR
Swanson 2006 (PATS) U.S. (Fair)	Mean age=4.4 years 74% male	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Setlik 2009 U.S. (Poor)	Amphetamine/DEX related calls increased to 476%, p=0.003 per year Prescriptions for amphetamine/DEX increased 133% (p=0.0004) for 3-19 yr olds and 141% (p≤0.0001 for 10-19 yr olds No. of teen amphetamine/DEX abuse calls per million prescriptions increased 140%(p=0.0005) Methamphetamine related calls decreased by 30% (p=0.003). Prescription for MPH increased 52%(p=0.0038) for 3-19 yr olds and 57% for 10-19 yr olds(p=0.0019) No. of teens MPH abuse calls per million prescription of MPH for 10-19 yr old decreased 55% (p=0.0001) % of patients with moderate, major effects, death in amphetamine/DEX vs MPH groups: 45% vs 37%p<0.001.	Funding for acquisition of IMS health national disease and therapeutics index prescription data supplied by RADARS system, a governmental non-profit operation of the Rocky Mountain Poison and Drug Center, Agency of Denver Health and Hospital Authority	
Spencer 2005 U.S. (Fair)	34 (24.6%) anorexia, MAS XR dose 10 mg n=8, 20mg n=10, 30 mg n=13, 40 mg n=3, 50 mg n=1, 60 mg n=2 34 (24.6%) weight loss, 2 patients discontinued treatment, MAS XR dose 10 mg n=3, 20 mg n=12, 30 mg n=15, 40 mg n=3, 50 mg n=2, 60 mg n=0 Mean body weight decreased by 2.4 kg (5.2 lbs) from baseline to endpoint, p<.0001 Decrease in body weight among MAS XR-naïve patients (-9.2 lbs, p<.0001) was greater than among MAS XR-continuous patients (-3.3 lbs, p=.0004) Magnitude of weight loss related to baseline weight, those >75th percentile at baseline lost the most weight (4.2 kg [9.2 lbs], p<.0001)	NR (possibly Shire Pharmaceuticals Inc.)	
Swanson 2006 (PATS) U.S. (Fair)	Mean growth rate slowed with treatment (p<.0001) For children who remained on medication (n=95) annual gain was 20.3% less than expected for height and 55.2% less than expected for weight	National Institute of Mental Health, University of California Irvine, Duke University Medical Center, NYSPI/Columbia University, New York University Child Study Center, University of California Los Angeles, and Johns Hopkins University	Greater than expected height and weight observed at baseline (p<.0001)

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Thompson 2006 (Poor)	Retrospective study	IR psychostimulant SR MPH Duration: Unclear. Study population consisted of patients taking IR psychostimulant any time between Feb 2002-Feb 2004 2 year period	Patients identified from computer database and personal case load records, February 2002-February 2004	103
Weisler 2005 U.S. (Fair)	Open-label extension study Setting: multicenter	MAS XR; Adderall XR®, 20-60 mg/day, after 1 month 179 (80.3%) = dose of 40 or 60 mg/day (mean dose NR) Duration: 24 months	NR	223
Weiss 1975 (Fair)	Retrospective cohort	Group 1: MPH mean=30mg/day Group 2: chlorpromazine mean=75mg/day Group 3: none Duration: Group 1: 51 months Group 2: 30 months	Hyperactive children initially evaluated by the psychiatry department of the Montreal Children's Hospital from 1962-1967 had been treated with MPH, chlorpromazine, or none (group 1, 2 and 3).	150
Weizman 1987 Israel (Fair)	Before-After, prospective	MPH 10.3 mg Duration: 9 weeks		32

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Thompson 2006 (Poor)	12 years 9 months (range 6-17 years) 83.5% male NR	Good response on IR psychostimulant: 88.6% Good response on switching to SR MPH: 64.9%, difference between both response significant p<0.001 % of people switching back to IR psychostimulant from SR MPH=27%, p<0.0001
Weisler 2005 U.S. (Fair)	Mean age=39.8 years (18-76) 59.3% male 90.5% White 5.0% Hispanic 2.7% Black 1.8% other	NR
Weiss 1975 (Fair)	Mean age= 7.96, 8.15 and 8.21 years (group 1, 2 and 3) Gender: NR Ethnicity: NR	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
Weizman 1987 Israel (Fair)	Mean age=8.8 years 81% male Race NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Thompson 2006 (Poor)	NR	NR (reported that there were no declarations of interest)	
Weisler 2005 U.S. (Fair)	7 (3.1%) discontinued due to a cardiovascular AE: 5 (2.2%) hypertension; MAS XR 20 mg/day, n=1; 40 mg/day, n=1; 60 mg/day, n=3 2 (0.9%) palpitations and/or tachycardia, MAS XR 40 mg/day, which resolved upon discontinuation Clinically insignificant increases in mean QTcB (corrected by Bazett's formula) (7.2 msec, p<.001) and QTcF intervals (2.9 msec, p=.009) at 24 months No subject exhibited QTcB interval >480 msec (QTcF [corrected by Fridericia's formula] >454 msec) 2 (0.9%) clinically significant abnormal ECGs; n=1 at baseline, abnormal T-wave and lengthened QT interval that resolved, n=1 left anterior hemiblock at month 3 and ongoing at month 24; neither subject withdrawn	NR	Rollover from short-term study divided into 3 groups for analysis: MAS XR naïve, MAS XR continuous, and MAS XR interrupted
Weiss 1975 (Fair)	NR	Ciba Pharmaceuticals	
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		

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Wernicke 2003 U.S. (Fair)	Pooled analyses The short-term QTc-interval and cardiovascular adverse events data were not reported in the original publications.	Atomoxetine maximum dosage of 2 mg/kg/day administered in two divided doses (mean dose NR) Duration: At least 1 year	Data from the following: (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.	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Wernicke 2003 U.S. (Fair)	Children/adolescents (n=550) Mean age=10.5 75.1% male 78.5% white Adults Mean age=41.1 64.9% male 90.8% white Long-term population Data NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Wernicke 2003 U.S. (Fair)	Baseline change in corrected (Friderida formulate) QT intervals: short-term treatment, atomoxetine vs placebo, p-value *Children (n=325 vs n=202):* QTcD, mean change at endpoint: -3.1 vs -4.4, NS QTcD, increase > 30msec: 2.2% vs 4.5%, NS QTcD, increase > 60 msec or > 500 msec: NR QTcB, mean change at endpoint: 1.5 vs -4.5, p=0.004 QTcB, increase > 30 msec: 6.2% vs 7.4%, NS QTcB, increase > 60 msec: 0.3% vs 1.0%, NS QTcB, increase > 500 msec: NR QTcF, mean change at endpoint: -5.3 vs -4.4, NS QTcF, increase > 30 msec: 1.8% vs 2.5%, NS QTcF, increase > 60 msec or > 500 msec: NR *Adults (n=257 vs n=257)* QTcD, mean change at endpoint: 0.6 vs 0.8, NS QTcD, increase > 30msec: 2.3% vs 3.5%, NS QTcD, increase > 60 msec or > 500 msec: NR QTcB, mean change at endpoint: 5.7 vs 0.6, p<0.001 QTcB, increase > 30 msec: 6.2% vs 4.7%, NS QTcB, increase > 60 msec: 0.0% vs 0.0%, NS QTcB, increase > 500 msec: NR QTcF, mean change at endpoint: -2.7 vs 0.9, p=0.008 QTcF, increase > 30 msec: 1.2% vs 2.7%, NS QTcF, increase > 60 msec or > 500 msec: NR Long-term treatment group: "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, atomoxetine vs placebo, p-value: *Children (n=340 vs n=207):* Palpitation:0.3% vs 0%, NS Tachycardia:0.9% vs 0%, NS Cardiac murmur: 0.6% vs 0%, NS Extrasystoles: 0% vs 0%, NA Sinus tachycardia: 0.6% vs 0%, NS Ventricular extrasystole: 0.3% vs 0%, NS Atrial hypertrophy: 0% vs 0%, NA Sinus bradycardia: 0% vs 0%, NA *Adults (n=269 vs n=263):* Palpitation: 3.7% vs 0.8%, p=0.037 Tachycardia: 1.5% vs 0.8%, NS Cardiac murmur: 0% vs 0%, NA Extrasystoles: 0.4% vs 0.4%, NS Sinus tachycardia: 0.4% vs 0%, NS Ventricular extrasystole: 0% vs 0%, NA Atrial hypertrophy: 0% vs 0.4%, NS Sinus bradycardia: 0% vs 0.4%, NS	Eli Lilly and Company	

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Wilens 2003; 2004; 2005 U.S. (Fair)	Non-randomized open-label trial Setting: 14 sites Non-comparative	MPH 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 Duration: 12 months	Children who had used OROS MPH in previous trials and were found to be responders.	436
Wilens 2005 U.S. (Fair)	Open-label extension study Setting: Multicenter	MAS XR flexible dosing 10-60 mg/day (mean dose ranged 29 mg/day at 1 month to 32 mg/day at 4 months, >80% subjects received 20-40 mg/day for the study duration) Duration: 6 months	NR	138

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Wilens 2003; 2004; 2005 U.S. (Fair)	Mean age 9.2 years 83% male 86% white 5.7% black 0.7% Asian 4.4% Hispanic	NR
Wilens 2005 U.S. (Fair)	Mean age 14.4 years (13-17) 71.0% male 72.0% White	NR

Evidence Table 9. Data abstraction of observational studies

Author, year
Country **Harms** **Funder** **Comments**

Wilens 2003; 2004; 2005
U.S.
(Fair)

Adverse event	N (%)	Withdrawals due to AE	Specific adverse events
Headache	102 (25.1)	1	Tics: New onset occurred in 23 (6.4%) of 359 subjects with no known history of tics.
Insomnia	60 (14.7)	5	
Appetite suppression	55 (13.5)	7	
Abdominal pain	31 (7.6)	1	
Twitching	31 (7.6)	7	Sleep: sleep quality was rated good/excellent for 71% of subjects (282/398) in month 1, and for 74% of remaining subjects (134/182) in month 12. LOCF analysis showed that 69% of subjects received a good/excellent sleep quality rating at end of study.
Aggravation reaction	10 (2.5)		
Somnolence	10 (2.5)	1	
Reaction unevaluable	9 (2.2)		
Anxiety	9 (2.2)		
Weight loss	8 (2.0)	1	
Emotional lability	8 (2.0)	1	
Hostility	8 (2.0)	2	
Nausea	7 (1.7)		
Dizziness	7 (1.7)		Vital signs: 5 developed hypertension. 1 withdrew; elevated systolic readings resolved with discontinuation.
Vomiting	6 (1.5)		
Nervousness	6 (1.5)		
Depression	6 (1.5)		
Asthenia	5 (1.2)		
Hypertension	5 (1.2)	1	Growth: Mean weight decreased by 0.1 kg over the first 3 months then increased over the remainder of the study. See table below.
Apathy	4 (1.0)		
Worsening of ADHD	NR	3	
Compulsive skin picking	NR	1	
Hallucinations	NR	1	

Growth	Baseline	Month 3	Month 6	Month 9	Month 12
Weight (kg)	34.2	34.1	34.5	35.6	36.8
Rate of change (kg/mo)	---	**-0.033**	+0.133	+0.366	+0.400
Height (cm)	137.1	138.4	139.6	140.8	142.3
Rate of change (cm/mo)	---	+0.43	+0.40	+0.40	+0.50

Most children were already MPH responders prior to entry into the study, and patients with known hypersensitivity to MPH were excluded.

McNeil Consumer & Specialty Pharmaceuticals

Wilens 2005
U.S.
(Fair)

1 (0.7%) tachycardia (124 bpm), MAS XR dose NR
1 (0.7%) pulse 115 bpm at 5 months, MAS XR 30 mg/day
2 (1.4%) postural hypotension, MAS XR dose NR
2 (1.4%) syncope, MAS XR dose NR

Decrease in QTcB interval from baseline (-4.6±19.9 msec) was statistically (p=.009), but not clinically, significant at 6 months

NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Study design	Drugs, dosage, duration of exposure	Sample time frame, data source	Sample size
Wilens 2005/Spencer 2006 U.S. (Poor)	Open-label extension study Setting: Multicenter, 14 sites	MPH; OROS® (for growth analysis: mean daily dose increased from 34.3 mg at baseline to 43.7 mg at month 21) Duration: 24 months	Subjects who had participated in one of the previous efficacy or pharmacokinetic studies of OROS MPH	407
Winterstein 2009 U.S. (Fair)	Retrospective cohort	MPH or MAS. Dosage NR. Follow-up time, months , mean (SD) amphetamine vs MPH users: 19.2 (18.8) vs 22.5 (23.8)	Time frame: July 1994 to June 2004 Data source: Florida Medicaid fee-for-service program	Amphetamine users: 12338 MPH users: 18238
Zeiner 1995 Norway (Fair)	Prospective cohort	Medicated (MPH 23 mg) vs unmedicated Mean duration: 634 days	Boys referred by general physicians, pediatricians, and school psychologists to a child psychiatric outpatient unit because of hyperactivity and attention problems. Time frame NR.	23

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Population characteristics	Efficacy/Effectiveness outcomes
Wilens 2005/Spencer 2006 U.S. (Poor)	Growth analysis only: Mean age 9.4 years (6-13) 83.7% male 87.1% White 5.6% Black 0.6% Asian 2.8% Hispanic 3.9% other	NR
Winterstein 2009 U.S. (Fair)	Age at first assignment to group: Range 8.3 to 9.2 years Male: 72% Ethnicity White:44 to 51% Black: 27.9 to 34.7% Hispanic: 14.4 to 16% Concomitant use of antidepressants: 14 to 21% Concomitant use of antipsychotics: 8 to 12.7% Congenital anomalies: 1.6% History of circulatory disease/symptoms: 1.9% Previous hospital admission for any cause: 2.9%	NR
Zeiner 1995 Norway (Fair)	Mean age 9.0 yrs 100% male Ethnicity NR	NR

Evidence Table 9. Data abstraction of observational studies

Author, year Country	Harms	Funder	Comments
Wilens 2005/Spencer 2006 U.S. (Poor)	Height was on average 0.23 cm less than expected at 21 months Weight was on average 1.23 kg less than expected at month 21, weight did not increase and BMI decreased slightly in the first 4 months Drug holidays did not significantly affect growth	McNeil Consumer & Specialty Pharmaceuticals	Growth analyzed in a subgroup of study subjects
Winterstein 2009 U.S. (Fair)	Emergency department visits for cardiac causes after adjusting for covariates Current use Adjusted HR 1.01(0.80 to 1.28), unadjusted RR 0.95 (95% CI0.74 to 1.21) Former use Adjusted HR 0.95 (95% CI 0.73 to 1.25), unadjusted RR 1.05 (0.78 to 1.42) Variables showing positive association with emergency department visits among current and former users Current use comparison use of bronchodilators: HR 1.88 (95% CI 1.40 to 2.53) use of antidepressants: HR 1.67 (95% CI 1.29 to 2.15) use of antipsychotics: HR 1.90 (95% CI 1.26 to 2.16) congenital anomalies: HR 3.12 (95% CI 2.22 to 4.38) history of circulatory disease or cardiac symptoms: HR 2.72 (95% CI 1.85 to 4.01) Switching patterns indicating intolerability % of patients on MPH switching to amphetamine 26.8% % of amphetamine users switching to MPH: 23.9%	Florida department of Health, Agency for Healthcare Administration Partly by grant received by Dr. Gerhard from Agency for healthcare Research and Quality U18HSO16097	
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	The Norwegian Medical Research Council, The Norwegian Public Health Association, and The Legacy of Haldis and Josef Andresen	

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased selection?	Loss to follow-up specified? If yes, low overall loss to follow-up? *(prior to Update 4)*	High overall loss to follow-up or differential loss to follow up? *(Update 4)*	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Barbaresi 2007	Yes	Yes 16.8% moved; 1.9% had unknown graduation drop out status	*Not rated*	Yes	Yes
Batterson 2005	Unclear	N/A - cross-sectional	*Not rated*	Yes	Yes
Brehaut 2003	Yes	No	*Not rated*	Yes	Yes
Charach 2006	No; only 87% of children who completed 12-month RCT were enrolled	No; Overall withdrawal rate of 25% at year 5	*Not rated*	Yes	Yes
Charles 1981	No; excluded 36 (36.7%)	N/A	*Not rated*	No	No
Coleman 2005	No	N/A - cross-sectional	*Not rated*	Unclear	No - limited
Donner 2007	No; select group of known responders and tolerant to drug	Yes; No - 441/2968 completed (15%)	*Not rated*	Yes	Yes
Faraone 2005	Unclear	Yes; No - 48% attrition	*Not rated*	Yes	Yes
Findling 2005	No	Yes; No: 4-w study: completion I 90%, C 82% 2-y study: overall 40%	*Not rated*	Yes	Yes
Forrester 2006	No; medical outcome only known for 53% of all human exposures	N/A - cross-sectional	*Not rated*	Yes	Yes
Gadow 1999	Yes	Yes; 5/34 (14.7%) lost to follow-up	*Not rated*	No	Yes
Garnier 2010	Unclear; screened all students at new student orientation; not clear if total sample was all new students or a selection of them	*Not rated*	High loss: 483/1253 who entered were analyzed (38.5%)	Yes	Yes

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating	Comments
Barbaresi 2007	Yes	No; controlled for age and grade	Yes	Fair	
Batterson 2005	Yes	No	None	Poor	
Brehaut 2003	Yes	Yes	Yes	Fair	
Charach 2006	Unclear who collected measurements and whether they were blinded to medication status	Yes	Yes	Poor	
Charles 1981	No	No	Yes	Fair/Poor	
Coleman 2005	Unclear	None	None	Poor	
Donner 2007	Unclear	NR	Yes; 15 weeks	Poor	Large single-group cohort study; low follow-up rate
Faraone 2005	Yes	NR	Yes; generally 6+ months	Poor	Open-label extension of RCT; high attrition and attrition related to weight deficit
Findling 2005	Unclear; ECGs were read at central office	NR	Yes; 2 years	Poor	Open-label extension of RCT; no comparison group and high attrition
Forrester 2006	Unclear who classified medical exposure	None	Yes	Poor	
Gadow 1999	Yes	Yes	Yes	Fair	
Garnier 2010	Potential for bias: trained interviewers, but face-to-face interviews and sensitive information, no verification	Yes	Yes	Poor	

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased selection?	Loss to follow-up specified? If yes, low overall loss to follow-up? *(prior to Update 4)*	High overall loss to follow-up or differential loss to follow up? *(Update 4)*	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Gau 2006	Yes; 88% or target recruited	No; attrition due to "not currently treated with" ADHD drug	*Not rated*	Yes	Yes
Goldman 2008	Unclear; all subjects w/ RS eligible	No	*Not rated*	Only RS	Yes
Gross 1976	No	No	*Not rated*	Yes	Yes
Gualtieri 1985	No	Yes	*Not rated*	No	No
Hechtman 1984	Yes	Yes; No	*Not rated*	Yes	No
Holick 2009	Yes	*Not rated*	No	Yes	Yes
Horrigan 2000	Yes	No	*Not rated*	No	No
Kemner 2006/Lage 2004	Yes	No	*Not rated*	Yes	Yes
Kemner 2006b (OROS MPH vs. TID IR MPH)	Yes	No	*Not rated*	Yes	Yes
Kratochvil 2001	Yes	Yes; 2/10 (20%) lost to follow-up	*Not rated*	No	No
Lage 2004	Yes	N/A	*Not rated*	Yes	Yes

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating	Comments
Gau 2006	Yes; questionnaires administer to patients and families	Yes; regression model of predictors for drug adherence; poor and good adherence groups compared; controlled for age, sex, education	Yes; 1 month	Fair	
Goldman 2008	Yes	Unclear; used case control sample based on demographics.	N/A; retrospective study of patients within a 5 year period	Fair/Poor	Retrospective case control study looked at RS only. Limited description of case control sample.
Gross 1976	Yes	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	Unclear	NR	Yes	Fair	
Hechtman 1984	Unclear	No	Yes	Fair	
Holick 2009	Unclear; medical record review was only possible for 77% of CVA's and 78% of TIA's, and resulting confirmations were less than 33%	Yes	Yes; mean=1.5 years	Fair	
Horrigan 2000	Unclear	NR	Yes	Fair	
Kemner 2006/Lage 2004	Yes	Yes; controlled for demographic characteristics, general health status, comorbid diagnoses associated with diagnosis of ADHD and use of ADHD medications	Yes	Fair	
Kemner 2006b (OROS MPH vs. TID IR MPH)	Yes	Yes; controlled for demographics, health status, comorbid diagnosis, and use of ADHD medications	Yes	Fair	
Kratochvil 2001	Yes	Yes	No	Fair	
Lage 2004	Yes	Yes	Yes	Fair	

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased selection?	Loss to follow-up specified? If yes, low overall loss to follow-up? *(prior to Update 4)*	High overall loss to follow-up or differential loss to follow up? *(Update 4)*	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Lee 2007	Unclear as to how many were eligible compared to how many were enrolled	Yes; Yes	*Not rated*	Yes	Yes
Lerer 1977	No; excluded 11 (41%) nonresponders	No	*Not rated*	Yes	No
Marcus 2005	Unclear	N/A	*Not rated*	Yes	Yes
Mattes 1983	No	No	*Not rated*	Yes	No
McAfee 2008	Unclear; database inclusion criteria does not specify new users	*Not rated*	Unclear; patients with less than one year of coverage excluded from analysis	Yes	Yes
McCarthy 2009	Yes; database; inclusion criteria specified	*Not rated*	No - response 100%	Yes	Yes
McGough 2005	No; only subjects with no prior clinically relevant AE in previous study were eligible	Yes; 74/568 (13%) were lost to follow up; 273/568 (48%) completed 24 months of treatment	*Not rated*	Yes	Yes
McNutt 1976a (preliminary report)/McNutt 1976b	Unclear; number of children in short-term studies NR	Unclear	*Not rated*	Yes	Yes
Miller-Horn 2008	No; first 150 entered into the database were included	N/A	*Not rated*	Yes	Yes
Millichap 1977	Yes	No	*Not rated*	Yes	No

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating	Comments
Lee 2007	Yes	N/A	Yes	Fair	
Lerer 1977	Unclear	NR	Yes	Fair	
Marcus 2005	Yes	Yes	Yes	Fair	
Mattes 1983	Yes	Yes	Yes	Fair	
McAfee 2008	Yes; reviewer blinded to ADHD diagnosis determined seizure diagnosis	Yes	Yes	Fair	
McCarthy 2009	Yes	No; descriptive statistics only for mortality; compared suicide rate in cohort to suicide rate in general population adjusted for age and sex only	Yes	Fair	
McGough 2005	Yes	NR	Yes; 24 months	Fair	Open-label extension of RCT
McNutt 1976a (preliminary report)/McNutt 1976b	Yes	Yes	Yes	Fair	
Miller-Horn 2008	Yes	NR	N/A; retrospective study of patients over a 24 month period	Fair	Open-label retrospective study
Millichap 1977	Yes	No	Yes	Fair	

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased selection?	Loss to follow-up specified? If yes, low overall loss to follow-up? *(prior to Update 4)*	High overall loss to follow-up or differential loss to follow up? *(Update 4)*	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Olfson 2007	Yes	No loss to follow-up	*Not rated*	Yes	Yes
Paternite 1999	No; excluded 24 (19.8%)	No	*Not rated*	Yes	Yes
Perwein 2006	Unclear; no data on recruitment	Yes; Yes - 65% completed acute phase (10w); long-term 34% (24 m); most withdrawals due to discontinuation of drug	*Not rated*	Yes	Yes
Pliszka 2006	Yes	Yes; No - 3-year analysis excluded 65% of patients	*Not rated*	Yes	Yes
Quinn 1975	No	Yes; 3/76 (3.9%) lost to follow up	*Not rated*	No	No
Rabiner 2009	Unclear; all sophomores and random sample of other classes at 2 universities invited to participate, but total sample not clear	*Not rated*	Possible bias: 28% of surveys at public university and 45% at private university were completed	Yes	Yes; self-administered web-based survey
Rao 1998	Yes	N/A	*Not rated*	Yes	No

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating	Comments
Olfson 2007	Yes	Yes; statistical analysis was done controlling for age, gender, treating specialist, other treated mental disorders, claims for other prescribed psychotropic medications, claims for ER and inpatient services in which the first listed diagnosis is mental disorder	Yes	Fair	
Paternite 1999	Yes	Yes	Yes	Fair	
Perwein 2006	Yes	NA (single-group study)	Yes; 24 months	Poor; high attrition rate	
Pliszka 2006	Yes	Adjusted for age and time	Yes	Poor	
Quinn 1975	Yes	NR	Yes	Fair	
Rabiner 2009	Outcomes not verified	No; descriptive statistics only	Yes	Poor	
Rao 1998	Yes	Yes	Unclear	Fair	

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased selection?	Loss to follow-up specified? If yes, low overall loss to follow-up? *(prior to Update 4)*	High overall loss to follow-up or differential loss to follow up? *(Update 4)*	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Safer 1972	No	Yes	*Not rated*	Yes	No
Safer 1973	Yes	No	*Not rated*	No	Yes
Safer 1975	Yes	No	*Not rated*	Yes	No
Sanchez 2005	Yes	N/A	*Not rated*	Yes	Yes
Satterfield 1979	Yes	No	*Not rated*	Yes	Yes
Schelleman 2011	Yes; all subjects meeting inclusion criteria were selected (time-frame not specified)	*Not rated*	No	Yes	Yes
Setlik 2009	No; calls to poison control centers used as proxy for estimating level of abuse (although unbiased sampling of calls- used all calls over an 8-year period)	*Not rated*	Final outcome determined in 64% of calls; no info on other missing data	Yes	Yes
Spencer 2005	No; select group of compliant subjects known to be tolerant to the drug	Yes; No - completion 76%	*Not rated*	Yes	Yes
Swanson 2006	Unclear	Yes; No - 67% completed	*Not rated*	Yes	Yes
Thompson 2006	Unclear; no data on recruitment	Yes; 5% data unavailable	*Not rated*	Unclear; had standardized form	No

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating	Comments
Safer 1972	No	NR	Yes	Fair	Main outcome (percentile change) uses two time points (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.
Safer 1973	No	Yes	Yes	Fair	
Safer 1975	Unclear	No	Yes	Poor	
Sanchez 2005	Yes	No	Yes	Fair	
Satterfield 1979	Yes	NR	Yes	Good	Adherence was assessed by monthly urinalysis.
Schelleman 2011	Yes	Yes; but because of low event rates, adjusted for confounders using exclusion	Yes	Fair	
Setlik 2009	Potential for bias: data collected by phone and not verified	No	Yes	Poor; no control for confounders in analysis of trends - data extrapolated from a sample of physicians to all prescriptions in the US	
Spencer 2005	No; spontaneously-reported AEs, reported to unblinded provider	NR	Yes; 6 months	Fair	Open-label extension of RCT
Swanson 2006	Yes	Yes; completers and study site	Yes; 4.4 years	Fair	Open-label extension of RCT
Thompson 2006	Unclear; no information on the form or data collection techniques	NA (single-group study)	Unclear	Poor	

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased selection?	Loss to follow-up specified? If yes, low overall loss to follow-up? *(prior to Update 4)*	High overall loss to follow-up or differential loss to follow up? *(Update 4)*	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?
Weisler 2005	No; only subjects with no prior clinically relevant AE in previous study were eligible	Yes; Yes - 44% completed	*Not rated*	Yes; cardiac only	Yes
Weiss 1975	No	No	*Not rated*	Yes	No
Weizman 1987	Unclear	Unclear	*Not rated*	Yes	Yes
Wernicke 2003	No	No	*Not rated*	Yes	Yes
Wilens 2003; 2004; 2005	No	Yes; 16/407 (3.9%) lost to follow-up; 289/407 (71%) completed 12 months of treatment	*Not rated*	Yes	Yes
Wilens 2005	No; low rate of inclusion into 6 month extension study	Yes; No - 80% completed 6 months of treatment	*Not rated*	Yes	Yes
Wilens 2005/Spencer 2006	Unclear	Yes; No - 71% completed 12 months (AEs measurement); 44% completed 21+ months for growth measures	*Not rated*	Yes	Yes
Winterstein 2009	Yes; database; inclusion criteria specified; 180 days without a prescription	*Not rated*	No	Yes	No
Zeiner 1995	No	Yes; 2/38 (5.3%) lost to follow-up	*Not rated*	Yes	No

Evidence Table 10. Quality assessment of observational studies

Author Year	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating	Comments
Weisler 2005	Yes	NR	Yes; 24 months	Fair	Analysis was from a 4-weel RCT and a 24-month open-label extension study
Weiss 1975	Unclear	NR	Yes	Fair	
Weizman 1987	Yes	No	No	Fair	
Wernicke 2003	Yes for ECG; unclear for adverse events	Unclear	Yes	Fair	
Wilens 2003; 2004; 2005	Yes	NR	Yes	Fair	Study selected for MPH responders, decreasing likelihood of AEs
Wilens 2005	Unclear; ECGs were read at central office	NR	Yes; 6 months	Fair	Open-label extension of RCT
Wilens 2005/Spencer 2006	Yes	NR	Yes; 21+ months	Poor	Open-label extension of RCT; no comparison group and high attrition
Winterstein 2009	No verification of outcomes reported	Yes	Yes	Fair	
Zeiner 1995	Unclear	Yes	Yes	Fair	

Evidence Table 11. Data abstraction of abuse and diversion studies

Author Year Country Trial name (Quality rating)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Fredericks 2005 (Poor)	Children 10-14 years with established ADHD taking methylphenidate	Maintenance doses were encapsulated for each participant (three participants with 10 mg, one with 20 mg and one with 30 mg) Total 3 weeks Participants were given MPH or placebo and were to take that except for the six sampling sessions where participants had a chance to experience both drugs and six choice sessions where participants had the opportunity to choose their preference (Methylphenidate or placebo or neither)	NR	Mean age=12 yrs Gender: 80% male Ethnicity: NR	All participants had current prescription for MPH for treatment of ADHD symptoms and have been taking immediate-release MPH treatment for at least 1 yr prior to the study
Oesterheld 1998 (Poor)	Native American child 5 to 12 years with full or partial fetal alcohol syndrome with ADHD	Methylphenidate 0.6 mg /kg 5 days-lactose placebo 5 days and vitamin C placebo 2 days off in between Total 3 weeks	None	Mean age=8.25 yrs Gender: 50% male Ethnicity: 100% Native American	2 boys full FAS 2 girls partial FAS

Evidence Table 11. Data abstraction of abuse and diversion studies

Author Year Country Trial name (Quality rating)	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/effectiveness outcomes	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Fredericks 2005 (Poor)	5	0/ 0/ 5	Differences between the number of MPH, Placebo, and Neither choices across participants were significant ($X^2 = 9.6$; $p < 0.01$). Three of five participants reliably chose MPH more often than placebo. MPH produced idiosyncratic patterns of participant-rated effects but failed to produce significant clinical effects.	NR	NR	NR	
Oesterheld 1998 (Poor)	4	NA	CPRS-48 Hyperactivity-Impulsivity scale: $F=4.34$, df 4, P< 0.05; the daydreaming attention scale was NS CTRS-39 Hyperactivity-Impulsivity scale: $F=6.42$, df 4, P<0.02	During active treatment: Decreased appetite: 75% Stomach ache: 50% Headache: 50%	Total: 0 Due to Aes: 0	U of South Dakota: USF-Minigrant 94 202-4590-005	

Evidence Table 12. Quality assessment of abuse and diversion studies

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Intent-to-treat analysis
Fredericks 2005	Yes; the order in which placebo and MPH were scheduled in the sampling sessions was counter-balanced across subjects and within-subjects across weeks	Yes	Yes; only 5 participants	Yes	Yes	Yes; medication dispensers blinded	Yes	NR
Oesterheld 1998	NR	Unclear	Yes; only 4 participants	Yes	Yes	Yes	Yes	NR

Evidence Table 12. Quality assessment of abuse and diversion studies

Author, Year	Post-randomization exclusions *(prior to Update 4)*	Maintenance of comparable groups *(Update 4)*	Loss to follow-up: differential/high *(prior to Update 4)*	Reporting of attrition, crossovers, adherence, and contamination *(prior to Update 4)*	Acceptable levels of crossovers, adherence, and contamination? *(Update 4)*	Quality Rating
Fredericks 2005	N	*Not rated*	No/No	N/A	*Not rated*	Poor; not sure how to rate this study
Oesterheld 1998	N	*Not rated*	No/No	N/A	*Not rated*	Poor; not sure how to rate this study