

Drug Class Review on Pharmacologic Treatments for ADHD

Final Report Update #2
Evidence Tables

November 2007



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

Marian S. McDonagh, PharmD
Kim Peterson, MS
Tracy Dana, MLS
Sujata Thakurta, MPA:HA

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

Copyright © 2007 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.



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

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

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

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed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

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

Author, year	Results	Method of adverse effects assessment
Pelham 1987	<p>Methylphenidate vs sustained release methylphenidate, t-test, p-value:</p> <p>Daily frequencies</p> <p>Following rules: 3.5 vs 4.3, t=1.8, p=NS</p> <p>Noncompliance: 3.4 vs 4.3, t=-2.5, p<0.05</p> <p>Positive peer behaviors=100.2 vs 95.8, t=0.8, p=NS</p> <p>Conduct problems: 0.3 vs 0.4, t=-0.4, p=NS</p> <p>Negative verbalizations=3.4 vs 4.8, t=-2.3, p<0.05</p> <p>N. of time outs/day: 0.5 vs 0.7, t=-1.2, p=NS</p> <p>Classroom</p> <p>% on task=95.2 vs 96.5, t=-0.6, p=NS</p> <p>% on following rules=93.9 vs 92.2, t=0.6, p=NS</p> <p>Timed math</p> <p>No. attempted=21.0 vs 21.7, t=-0.5, p=NS</p> <p>% correct=93.4 vs 94.4, t=-0.5, p=NS</p> <p>Timed reading</p> <p>No. attempted=19.8 vs 18.2, t=1.4, p=NS</p> <p>% correct=79.8 vs 77.9, t=0.4, p=NS</p> <p>Seatwork</p> <p>% completion=86.1 vs 89.1, t=-0.9, p=NS</p> <p>% correct=83.7 vs 82.9, t=0.3, p=NS</p> <p>Teacher rating: 1.9 vs 3.4, t=-1.3, p=NS</p> <p>Counselor rating: 106.4 vs 105.9, t=0.1, p=NS</p> <p>Positive daily report card (% of days received): 83.2 vs 81.8, t=0.2, p=NS</p> <p>Observed interactions</p> <p>Positive peer: 97.9 vs 95.2, t=1.6, p=NS</p> <p>Negative peer: 1.4 vs 1.5, t=-0.2, p=NS</p> <p>No interactions: 0.7 vs 3.3, t=-1.8, p=NS</p>	NR

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

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

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

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

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

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

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

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

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

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

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

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

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

Author, year	Results	Method of adverse effects assessment
Pelham 2001 Fair	<p>Placebo / tid IR MPH / Concerta, p-value = MPH IR vs Concerta</p> <p><u>Natural setting</u></p> <p>Teacher ratings</p> <p>Inattention/overactivity: 10.34 vs 5 vs 4.69, p=NS; Oppositional/defiant: 5.09 vs 1.99 vs 1.81, p=NS</p> <p>Abbreviated Conners: 16.40 vs 7.4 vs 7.82, p=NS; Peer interactions: 4.29 vs 4.03 vs 3.41; p=NS</p> <p>Global effectiveness: NS on any classification</p> <p>Daily report card (% positive): 61.17 vs 84.36 vs 86.06</p> <p>Parent ratings</p> <p>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</p> <p>Abbreviated Conners: 19.91 vs 11.41 vs 9.49; p=0.05</p> <p>Global effectiveness: Poor: 73.5% vs 8.8% vs 5.9%; p=NS; Fair: 22.1% vs 26.5% vs 27.9%, p=NS</p> <p>Good: 2.9% vs 50.0% vs 39.7%, p=NS; Excellent: 1.5% vs 14.5% vs 26.5%, p=NS</p> <p>(p=NS for all remaining comparisons of tid IR MPH vs Concerta)</p> <p><u>Recreational Activities -- Counselor measures</u></p> <p>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</p> <p>1:25-1:55: 5.87 vs 2.17 vs 2.39; 4:35-5:00: 5.21 vs 2.84 vs 2.53</p> <p>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</p> <p>1:25-1:55: 6.25 vs 0.98 vs 2.45; 4:35-5:00: 4.76 vs 2.83 vs 1.58</p> <p>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</p> <p>1:25-1:55: 56.13 vs 81.25 vs 74.22; 4:35-5:00: 58.82 vs 76.43 vs 80.73</p> <p>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</p> <p>1:25-1:55: 8.96 vs 2.17 vs 3.47; 4:35-5:00: 8.91 vs 4.61 vs 2.86</p> <p><u>Recess measures (means)</u></p> <p>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;</p> <p>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</p> <p><u>Laboratory sessions (means) (overall daily measures)</u></p> <p>Behavior frequencies</p> <p>Following rules: 47.5% vs 60.2% vs 61.3%; Noncompliance: 5.76 vs 2.73 vs 2.14</p> <p>Interruption: 21.6 vs 10.5 vs 10.58; Complaining/whining: 15.45 vs 6.95 vs 6.67</p> <p>Positive peer behaviors: 10.52 vs 9.86 vs 9.20; conduct problems: 3.81 vs 1.53 vs 0.60</p> <p>Negative verbalizations: 18.27 vs 9.29 vs 7.14</p> <p>Teacher rating-- Inattention/overactivity: 5.01 vs 2.75 vs 2.59; Oppositional/defiant: 2.18 vs 1.19 vs 1.30</p> <p>Abbreviated Conners: 7.03 vs 4.03 vs 3.75; Peer interactions: 0.24 vs 0.15 vs 0.15</p> <p>Counselor rating-- Inattention/overactivity: 7.95 vs 6.31 vs 6.10; Oppositional/defiant: 3.63 vs 2.58 vs 2.36</p> <p>Abbreviated Conners: 12.70 vs 9.91 vs 9.26; Peer interactions: 0.77 vs 0.56 vs 0.49</p>	<p>Spontaneous reports; parents completed questions regarding AEs, sleep quality, appetite, and tics; sleep quality for the week was rated as poor, fair, good, or excellent; food intake for the week relative to usual food intake was rated as less, usual amount, or more</p>

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

Author, year	Adverse Effects Reported
Pelham 2001	Placebo vs qd Concerta vs tid IR MPH
Fair	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%)

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

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

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

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

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

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

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

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

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

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Cox 2004	Inattentive type=4(66.7%) Combined type=2(33.3%) Proportion taking medication for ADHD at baseline NR Mean baseline dose of MPH NR	NR/NR/7	1 (14.3%) withdrawn/0 lost to fu/analyzed=6
Wolraich 2001 United States	ADHD Diagnosis 73.4% combined 19.5% inattentive 7.1% hyperactive/impulsive Previous stimulant therapy 20.2% None 6.4% Not in previous 4 weeks 5.7% Non-MPH 67.7% MPH	Screened=500/E nrolled=405/Ran domized=312	Withdrawn=206 (66%)/Lost to follow- up=1(0.3%)/Analyzed=2 77 (MPH n=94, MPH OROS n=94, Placebo n=89)

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

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

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

Author, year	Adverse Effects Reported
Cox 2004	NR
Fair	
Wolraich 2001 United States	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
Fair	

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

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

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

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

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

Author, year	Interventions and total daily dose Duration Dosing schedule
Whitehouse 1980 United States	Standard methylphenidate 20 mg (twice daily) Sustained-release methylphenidate 20 mg (once daily) Duration=2 weeks Dosing schedule: 30 minutes prior to breakfast; 30 minutes before lunch
Steele 2006 Canada	<p>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.</p> <p>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.</p>

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

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

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

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

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

Author, year	Results	Method of adverse effects assessment
Whitehouse 1980 United States	<p>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</p>	NR
Steele 2006 Canada	<p>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)</p> <p><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</p>	Safety assessments collected included adverse events, physical examination, vital signs, and body weight

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

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

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

Author, year	Total withdrawals; withdrawals due to adverse events	Comments
Whitehouse 1980 United States	4 (11.8%) (group assignment NR) No withdrawals due to adverse events	

Fair

Steele
2006
Canada

Total =24 (16.6%)
AEs=8 (5.5%)

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

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

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

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

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

Author, year	Run-in/Washout Period	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity
Findling 2006 Australia, Canada, United States	NR	NR	<p>Primary Outcome Measure: the inattention/ overactivity (I/O) component of the overall Teacher's IOWA Conners' Questionnaire obtained from the SNAP-IV questionnaire</p> <p>Other Measures: IOWA Conners' Rating Scale, the 40-item SNAP-IV (which includes the IOWA Conners' Rating scale as a subscale), the Clinical Global Impression (CGI) Scale and the CGI Improvement scale, the Parent's Global Assessment (PGA)</p>	<p>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</p>

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

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

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

Author, year	Results	Method of adverse effects assessment
Findling 2006 Australia, Canada, United States	<p data-bbox="415 269 932 293">Difference from placebo (95% CI) for MPH-IR vs EqXL</p> <p data-bbox="415 293 1125 318"><u>Teacher's Ratings: I/O component of 10-item IOWA Conners' Rating Scale</u></p> <p data-bbox="415 318 869 342">1-week: -2.4 (-3.36, -1.39) vs -1.9 (-2.87, -0.91)</p> <p data-bbox="415 342 869 367">2-week: -2.6 (-3.70, -1.43) vs -2.4 (-3.58, -1.31)</p> <p data-bbox="415 367 869 391">3-week: -3.4 (-4.53, -2.26) vs -3.1 (-4.26, -2.00)</p> <p data-bbox="415 423 1125 448"><u>Teacher's Ratings: O/D component of 10-item IOWA Conners' Rating Scale</u></p> <p data-bbox="415 448 869 472">1-week: -1.7 (-2.54, -0.38) vs -1.5 (-2.32, -0.62)</p> <p data-bbox="415 472 869 496">2-week: -1.9 (-2.81, -0.93) vs -1.8 (-2.69, -0.81)</p> <p data-bbox="415 496 869 521">3-week: -2.4 (-3.36, -1.38) vs -2.5 (-3.47, -1.48)</p> <p data-bbox="415 553 1104 578"><u>Parent's Ratings: I/O component of 10-item IOWA Conners' Rating Scale</u></p> <p data-bbox="415 578 869 602">1-week: -2.3 (-3.31, -1.22) vs -1.3 (-2.33, -0.23)</p> <p data-bbox="415 602 869 626">2-week: -2.6 (-3.65, -1.53) vs -1.9 (-2.97, -0.86)</p> <p data-bbox="415 626 869 651">3-week: -3.0 (-4.09, -1.85) vs -1.7 (-2.78, -0.54)</p> <p data-bbox="415 683 1115 708"><u>Parent's Ratings: O/D component of 10-item IOWA Conners' Rating Scale</u></p> <p data-bbox="415 708 869 732">1-week: -2.1 (-3.22, -1.04) vs -1.8 (-2.89, -0.71)</p> <p data-bbox="415 732 869 756">2-week: -2.5 (-3.64, -1.30) vs -2.1 (-3.26, -0.92)</p> <p data-bbox="415 756 869 781">3-week: -2.3 (-3.46, -1.16) vs -1.6 (-2.74, -0.44)</p>	Throughout study, safety assessments were performed including hematology measures, biochemistry tests, urinalysis, weight, vital signs, and physical examination. Reported AE's were recorded giving duration, intensity and relationship to study drug, action taken, outcome, and seriousness. In addition, parents and teachers completed the Barkley Side Effects Rating Scale on same days as respective SNAP-IV ratings

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

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

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

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

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

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

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

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

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

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

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

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Gau 2006 Taiwan	<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)	NR/NR/64	0/0/64

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

Author, year	Results	Method of adverse effects assessment
Gau 2006 Taiwan	<u>Conners' Teaching Rating Scale-Revised, Short Form-C, Day 13-Baseline, mean (SD) OROS vs. IR:</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>Conners' Teaching Rating Scale-Revised, Short Form-C, 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) <u>Conners' Parent Rating Scale-Revised: Short Form-C, Day 13-Baseline, mean (SD) OROS vs. IR:</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>Conners' Parent Rating Scale-Revised: Short Form-C, Day 27-Baseline, mean (SD) OROS vs. IR:</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) <u>SKAMP, Day 13-Baseline mean (SD) OROS vs. IR:</u> Attention: -1.77 (3.16) vs. -1.72 (4.08) Depoement: -2.77 (4.05) vs. -3.25 (4.13) <u>SKAMP, Day 27-Baseline mean (SD) OROS vs. IR:</u> Attention: -3.71 (3.39) vs. -2.98 (5.29) Depoement: -4.65 (5.53) vs. -4.41 (6.71)	Barkley's Side Effects Questionnaire (BSEQ) was used to measure side effects of MPH. Vital signs (including systolic BP & pulse rate) were checked and any AE was documented if any occurred at each visit.

At final assessment, OROS group had greater proportion of subjects veing very much or much

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

Author, year	Adverse Effects Reported
Gau 2006 Taiwan	<p data-bbox="415 269 1121 318"><u>Percentage of side effects with increased BSEQ score from baseline, day 27, OROS vs. IR MPH:</u></p> <p data-bbox="415 321 842 342">Decreased appetite: 46.9 vs. 59.4 (p=0.316)</p> <p data-bbox="415 345 873 367">Insomnia/sleep trouble: 40.6 vs. 46.9 (p=0.614)</p> <p data-bbox="415 370 789 391">Stomachache: 31.3 vs. 25.0 (p=0.578)</p> <p data-bbox="415 394 753 415">Headache: 21.9 vs. 34.4 (p=0.266)</p> <p data-bbox="415 418 730 440">Nightmares: 7.8 vs. 25.0 (0.351)</p> <p data-bbox="415 443 867 464">Uninterested in others: 28.1 vs. 40.6 (p=0.292)</p> <p data-bbox="415 467 716 488">Irritable: 9.4 vs. 21.9 (p=0.169)</p> <p data-bbox="415 492 743 513">Dry mouth: 31.3 vs. 17.2 (p=0.79)</p> <p data-bbox="415 516 936 537">Sad/unhappy, prone to crying: 31.3 vs. 43.8 (p=0.302)</p> <p data-bbox="415 540 732 561">Anxious: 18.7 vs. 31.3 (p=0.248)</p> <p data-bbox="415 565 800 586">Bites fingernails: 18.7 vs. 25.0 (p=0.545)</p> <p data-bbox="415 589 753 610">Drowsiness: 7.8 vs. 18.8 (p=0.741)</p> <p data-bbox="415 613 905 634">Tics or nervous movements: 7.8 vs. 18.8 (p=0.741)</p> <p data-bbox="415 691 926 712">No difference in vital signs on day 28 between groups</p>

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

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

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

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

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

Author, year	Interventions and total daily dose Duration Dosing schedule
Dopfner 2004 Germany	Medikinet-Retard (methylphenidate ER) qd Methylphenidate IR (MPH IR) bid Placebo
designed as a non-inferiority trial	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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Author, year	Results	Method of adverse effects assessment
<p>Extended release formulations of Methylphenidate</p>		
<p>Lopez 2003</p>	<p>MPH SODAS 20mg vs MPH OROS 18mg vs MPH OROS 36mg vs Placebo; p-values reflect comparison to MPH SODAS</p>	<p>NR</p>
<p>Fair</p>	<p><u>Mean change from baseline for SKAMP-attention</u> 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 <u>Mean change from baseline for SKAMP-deportment</u> 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 <u>Mean change from baseline for SKAMP-combined</u> 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) <u>Math test-attempted</u> 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 <u>Math Test Correct</u> 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</p>	

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

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

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

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

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

Author, year	Study Design Setting	Eligibility criteria	Comorbidity
Swanson 2004 Sonuga-Burke 2004 United States	RCT, DB, crossover multicenter	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 sign measurements, and by clinical laboratory assessments. Children also had to demonstrate the ability to swallow PLA study-treatment capsules whole and without difficulty.	~25% had a comorbid condition, with anxiety and ODD the most frequently reported conditions
COMACS Study			

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

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

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

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

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

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

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

Author, year	Results	Method of adverse effects assessment
Swanson 2004 Sonuga-Burke 2004 United States	Effect sizes: Metadate CD® vs Concerta® <u>SKAMP deportment</u> <u>Hours post-dose</u> 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	Adverse events reported by patient, parent, or guardian were characterized by an investigator as being mild (requires minimal or no treatment), moderate (result in low level inconvenience or concern) or severe (interrupt a patient's usual daily activity and may require drug or other therapy); parent or guardian completed the Barkley Side Effect Rating Scale
COMACS Study	<u>SKAMP attention</u> 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	
	<u>PERMP - # correct math problems</u> 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	

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

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

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

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

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

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

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

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

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

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

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

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

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

Author, year	Results	Method of adverse effects assessment
Silva 2005 United States	<p>Mean (SD) Postdose Scores (ER-MPH 20mg/ER-MPH 40mg/OROS-MPH 18mg/OROS-MPH 36mg/placebo)</p> <p><u>SKAMP-Attention (hours postdose)</u></p> <p>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)</p> <p><u>SKAMP-Depotment (hours postdose)</u></p> <p>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)</p>	<p>During each lab classroom day, vital signs and AE's were assessed. All AE's were recorded and described in terms of start and stop dates, severity of event, relationship to study drug, and any action taken for the event.</p>

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

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

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

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

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

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

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

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

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

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

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

Author, year	Other population characteristics (mean scores)	Screened/ eligible/ enrolled	Withdrawn/ lost to fu/analyzed
Other comparisons to methylphenidate			
Conners, 1980	NR	88/NR/60	NR/NR/60

Stephens 1984 United States	ACRS mean score=17.9	NR/NR/31	NR/NR/NR
Poor quality			

