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.
# TABLE OF CONTENTS

**Evidence Tables**

- Evidence Table 1. Placebo-controlled trials in preschool children and adolescents ..........3  
  Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents. .................................................................57  
- Evidence Table 3. Head to Head trials in children with ADHD ........................................66  
- Evidence Table 4. Quality assessment of head to head trials in children with ADHD ..........226  
- Evidence Table 5. Placebo-controlled trials in children ..................................................256  
- Evidence Table 6. Quality of placebo-controlled trials in children .................................391  
- Evidence Table 7. Long-term efficacy trials .................................................................412  
- Evidence Table 8. Quality in long-term efficacy trials ...................................................436  
- Evidence Table 9. Head to Head trials in adults with ADHD ..........................................442  
- Evidence Table 10. Quality assessment of head to head trials in adults with ADHD .........457  
- Evidence Table 11. Placebo-controlled trials in adults with ADHD ...............................461  
- Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD ..........................................................533  
- Evidence Table 13. Observational Studies - Functional Outcomes ..............................549  
- Evidence Table 14. Quality assessment of observational studies: Functional Outcomes ..........................................................564  
- Evidence Table 15. Observational studies - Long term safety ......................................568  
- Evidence Table 16. Quality of observational studies of long-term safety .........................613
**Evidence Table 1. Placebo-controlled trials in preschool children and adolescents**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schleifer 1975</td>
<td>(Fair)</td>
<td>RCT DB crossover</td>
<td>Preschool children diagnosed as hyperactive participated in this study</td>
<td>NR</td>
</tr>
</tbody>
</table>
| Barkley 1988    | (Fair)         | RCT DB crossover          | 1. Parent and/or teacher complaints of short attention span, poor impulse control and restlessness  
2. Age of onset of problem behavior prior to 6 years  
3. A duration of problem behavior for at least 12 months  
4. Scores on the Hyperactivity Index of the Conners Parent Rating Scale and the Werry-Weiss-Peters Activity Rating Scale greater than two SDs above the mean for same-age, same-sex normal children  
5. Scores on the Home Situations Questionnaire indicating that the child posed behavior problems in at least eight of the 16 situations described on the questionnaire to establish pervasiveness of behavior problems  
6. Absence of epilepsy, severe language delay, deafness, blindness, autism, psychosis or gross brain damage as established through developmental/medical histories and observation of the children | NR           |
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Interventions and total daily dose</th>
<th>Duration</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schleifer</td>
<td>1975 (Fair)</td>
<td>Methylphenidate: 2.5 mg - 20mg q.a.m and 10mg at lunch (mean dose = 5mg bid)</td>
<td>14-21 days</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td>Barkley</td>
<td>1988 (Fair)</td>
<td>Methylphenidate 0.15mg/kg bid or 0.5mg/kg bid</td>
<td>7-10 days for each condition (baseline, placebo, low dose, high dose)</td>
<td>2 days/NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schleifer</td>
<td>1975</td>
<td>Observation, Hyperactivity Rating Scale</td>
<td>Mean age=4.08 years</td>
<td>Gender: 89.3% male</td>
<td>Ethnicity: NR</td>
</tr>
<tr>
<td>(Fair)</td>
<td></td>
<td>Timing: before and after the intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barkley</td>
<td>1988</td>
<td>A free play (20 mins) and 5 task (20 mins total): mother-child interactions were videotaped and separate coding of the interactions was done using the Response Class Matrix.</td>
<td>Mean age=3.9 years</td>
<td>Gender: 70.3% male</td>
<td>Ethnicity: NR</td>
</tr>
<tr>
<td>(Fair)</td>
<td></td>
<td>Timing: the last day of each drug condition</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/ eligible/ enrolled</th>
<th>Number withdrawn/ lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schleifer</td>
<td>1975 (Fair)</td>
<td>Mean IQ=102 (86-124) Hollingshead scale (socioeconomic class): Mean=2.5</td>
<td>NR/NR/28</td>
<td>0/2/26</td>
</tr>
<tr>
<td>Barkley</td>
<td>1988 (Fair)</td>
<td>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)</td>
<td>NR/NR/27</td>
<td>0/0/27</td>
</tr>
</tbody>
</table>
# Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schleifer</td>
<td>1975 (Fair)</td>
<td>Hyperactivity Rating Scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pre: active: placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;True&quot; Hyperactives (n=10): 50.80: 40.30:47.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;Situational&quot; Hyperactives: (n=16): 46.66: 32.75: 42.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-way ANOVA (group x condition x order)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Active medication: F=29.09; p&lt;0.01</td>
</tr>
<tr>
<td>Barkley</td>
<td>1988 (Fair)</td>
<td>Pairwise Comparison:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Free play- only the low dose condition was significantly reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>as compared with the placebo condition, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Task interaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-compliance: 15% improvement in high dose compared with placebo, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-compete: 45% decrease occurred in off-task, or competing, behavior</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in high dose compared with placebo, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others: NS</td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preschool children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schleifer</td>
<td>1975 (Fair)</td>
<td>NR</td>
<td>NR</td>
<td>0</td>
<td>a tend (p&lt;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.</td>
</tr>
<tr>
<td>Barkley</td>
<td>1988 (Fair)</td>
<td>reported by mother</td>
<td>a tend (p&lt;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.</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
</table>
| Musten 1997           | RCT DB crossover     | 1. A diagnosis of ADHD based on DSM-III-R  
2. A score greater than 1 on 8 out of 14 DSM-III-R items  
3. A standard score greater than or equal to 80 on the Peabody Picture Vocabulary Test (PPVT)  
4. A score equal to or above 1.5 SD above the age and sex mean of the Hyperactivity Index of the Conners Parent Rating Scale-Revised.  
5. Attention span of less than 88 seconds on the parent-supervised attention task.  
6. Parent and children were fluent in English  
7. Subjects did not have any sensory or physical disatilities, developmental disorders, neurologic disease, or obvious central nervous system dysfunction as assessed by a pediatrician.  
8. Subjects who had received methylphenidate were considered for the study if they had received methylphenidate for less than 6 months and if the daily dosage administered was less than the mean of dosage used in the current study. | NR |
# Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Interventions and total daily dose</th>
<th>Duration</th>
<th>Dosing schedule</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musten</td>
<td>1997</td>
<td>methylphenidate 0.3mg/kg or 0.5mg/kg, bid</td>
<td>Duration: 7-10 days for each condition (placebo, low dose, high dose)</td>
<td>NR</td>
<td>2 days/ NR</td>
<td>NR</td>
</tr>
<tr>
<td>Firestone</td>
<td>1998 (Fair)</td>
<td>Duration: NR</td>
<td>Timing: NR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musten 1997</td>
<td>Cognitive measures (Gordon Diagnostic System Delay and Vigilance Tasks) Behavior rating (CPRS-R) Observed behaviors</td>
<td>Mean age=4.84 years</td>
<td>Gender: 83.9% male</td>
<td>NR</td>
</tr>
<tr>
<td>Firestone 1998</td>
<td>(Fair) Time on-Task Productivity Timing: at the end of the each treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musten</td>
<td>1997</td>
<td>Peabody Picture Vocabulary Test (standard score)=99.26(14.41)</td>
<td>109(43 refused, 64 agreed)</td>
<td>4/6/31</td>
</tr>
<tr>
<td>Firestone</td>
<td>1998 (Fair)</td>
<td>Diagnostic Interview for Children and Adolescents (number)=12.03(1.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Swansonm Nolan and Pelham Checklist (number)=11.48(1.91)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conners Hyperactivity Index (T score)=84.61(9.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Attention Task-Supervised (sec)=30.43(10.36)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musten</td>
<td>1997</td>
<td>Cognitive tasks:</td>
</tr>
<tr>
<td>Firestone</td>
<td>1998 (Fair)</td>
<td>Gordon Delay: no. correct, P&lt;L, P&lt;H, p&lt; 0.001; Efficiency ratio, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gordon Vigilance: no. correct, P&lt;L, P&lt;H, p&lt;0.01; commission errors, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parent Rating Scale:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conners: learning, P&gt;L, P&gt;H, L&gt;H, p&lt;0.001; Conduct, P&gt;L, P&gt;H, p&lt;0.001; Hyperactivity Index, P&gt;L, P&gt;H, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observed behaviors:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Child compliance Task: %compliance, NS; Dot-to-Dot %compliance, NS; Cancellation Task %compliance, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time on-Task: Dot-to-Dot Task time, P&lt;H, L&lt;H, p&lt;0.001; Cancellation task time, P&lt;H, L&lt;H, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Productivity: Dot-to-Dot Task patterns correct, NS; Cancellation Task rows correct, P&lt;H, L&lt;H, p&lt;0.01</td>
</tr>
</tbody>
</table>
Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musten 1997</td>
<td>Side Effects Rating Scale (17 items)</td>
<td>placebo: low dose: high dose (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firestone 1998 (Fair)</td>
<td></td>
<td>Temperament</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irritable: 81:75:38, P&gt;H, L&gt;H, p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sad/unhappy: 47:56:84, P&lt;H, L&lt;H, p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>prone to crying: 56:66:56, NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxious: 66:72:12, P&gt;H, L&gt;H, p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Euphoric/unusually happy: 19:25:6, NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temperament</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia or trouble sleep: 59:62:42, P&gt;H, L&gt;H, p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nightmares: 28:31:62, P&lt;H, L&gt;H, p&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stares a lot or daydreams: 47:47:52, NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased appetite: 25:56:81, P&lt;L, P&lt;H, L&lt;H, p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stomachaches: 31:38:22, NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headaches: 18.75:21.88:37.50, NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drowsiness: 12.50:25:65.63, P&lt;H, L&lt;H, p&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bites fingernails: 12.5:15.63:28.13, NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness: 0:3:13:3.13, NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tics or nervous movements: 3.13:9.38:12.50, NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sociability</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Talks less with others: 21.88:34.38:50, P&lt;H, p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uninterested in others: 31.25:37.5:75, P&lt;H, L&lt;H, p&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conners</td>
<td>1975 (Poor)</td>
<td>RCT DB</td>
<td>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, &quot;driven&quot; type of behavior, destructiveness of property, and aggressive 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)</td>
<td>80% of the children showed mild to moderate over-all dysfunction  0% was found to have major(focal) symptomatology  63% were found to have mild to moderate speech and language dysfunction  0% had marked movement disorders (synkinesis, dystonis, tremor, tics), but a majority had difficulty with gross body control.  over 80% of the mothers regarded the children as overactive during their first two years of life</td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
</table>
| Conners 1975 | methylphenidate  
Starting dosage: 5mg, bid (adjusted twice weekly)  
mean dose: 11.8(6.9)mg/day  
Duration: 6 weeks  
Timing: before the morning and midday meals | NR/NR                | NR                      |
## Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conners</td>
<td>1975</td>
<td>93-item behavior symptom list (before and after treatment) filled by parents. Clinical evaluation (week 2, 4, 6 after treatment): the Merrill-Palmer Intelligence Scale, the Beery-Buktenica Visual Motor Integration Test (VMI), the Flowers-Costello Test of centrak Auditory Abilities, the Meeting Street School Screening Test (MSST), Continuous Performance Test (CPT), the Harris-Goodenough Draw-a-Man Test, and Kagan's Matching Familiar Figures Test, Seat activity</td>
<td>Mean age=4.81 years</td>
<td>74.6%</td>
<td>100% white</td>
</tr>
</tbody>
</table>

Mean age=4.81 years
Gender: 74.6% male
Ethnicity: 100% white
Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conners 1975 (Poor)</td>
<td>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</td>
<td>NR/66/59</td>
<td>3/0/56</td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conners</td>
<td>1975 (Poor)</td>
<td>Parent rating:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Selected 18 items to be most related to hyperkinesis were analyzed, 4 out of 18 were significant improved in the drug group:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>disturbs other children, p&lt;0.03; restless or overactive, p&lt;0.01; throws himself around, p&lt;0.05; always climbing, p&lt;0.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Activity chair: seat movement decrease, p&lt;0.05; seat rotations, NS; feet movement, NS; total score, NS.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical evaluation (n=23, MPH=8, placebo=15):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSST: motor patterning improvement, NS; visual-perceptual-motor scores improvement, p&lt;0.025; language raw score improvement, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VMI: visual-perceptual-motor integration improvement, p&lt;0.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPT: reduction in errors of omission, NS; reduction in errors of commission, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Merrill-Palmer Intelligence Test: score improvement, p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Harris-Goodenough Draw-a-Man Test: IQ gain score improvement, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MFFT: NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flowers-Costiello Test of Central Auditory Abilities: total score, NS; competing messages test, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effects on Cortical Evoked Responses: increased amplitude for all visual and auditory amplitudes in drug condition, p&lt;0.05</td>
</tr>
</tbody>
</table>
**Evidence Table 1. Placebo-controlled trials in preschool children and adolescents**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conners</td>
<td>1975</td>
<td>Weight, BP, self-report</td>
<td>weight: NS</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td></td>
<td>BP: methylphenidate&gt;placebo, p&lt;0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
</table>
| Brown 1988 (Fair)     | RCT DB crossover     | 1. Receive a sexual maturity rating of at least 3 to thereby ensure postpubertal status  
2. Diagnosed as having a long history of symptoms associated with attention deficit disorder based on DSM-III  
3. Obtained a score of at least 15 on the Abbreviated Conners Teacher Rating Scale | NR |
| Pelham 1991 (Fair)    | RCT DB crossover     | Received a primary diagnosis of ADHD | 15 met or exceeded criteria for Oppositional/Defiant Disorder (ODD) or Conduct Disorder (CD) based on DSM-III-R |
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Interventions and total daily dose</th>
<th>Duration</th>
<th>Dosing schedule</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown 1988 (Fair)</td>
<td></td>
<td>methylphenidate 0.15mg/kg, 0.3mg/kg or 0.5mg/kg, bid (mean=4.38mg, 12.55mg, 21.28mg)</td>
<td>14 days</td>
<td>8am and 12pm</td>
<td>none of the subjects had been treated with stimulants during the year preceding the study/ NR</td>
<td></td>
</tr>
<tr>
<td>Pelham 1991 (Fair)</td>
<td></td>
<td>methylphenidate 0.3mg/kg to the nearest 1.25mg, bid</td>
<td>4-11 days</td>
<td>morning at breakfast and midday</td>
<td>2 weeks/ NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Final Report Drug Effectiveness Review Project
## Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Adolescent Method of Outcome Assessment and Timing of Assessment</th>
<th>Mean age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>1988 (Fair)</td>
<td>Behavioral (at the end of each 2-week trial)</td>
<td>13.5</td>
<td>100% male</td>
<td>black</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conners Parent Rating Scale-Revised (CPRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abbreviated Conners Parent (ACP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teacher Hyperactivity Index (ATR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADD/H Comprehensive Teacher Rating Scale (ACTeRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Attention and impulsivity (1 hour after medication)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Matching Familiar Figures Test (MFFT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gordon Diagnostic System (GDS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Academic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arithmetic task</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physiological (at least 1 hour after medication)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side Effect Rating Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelham</td>
<td>1991 (Fair)</td>
<td>Daily behavior-modification point system</td>
<td>12.59</td>
<td>100% male</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teacher-recorded classroom measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teacher and counselor Conners rating scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily child's individual behavior and academic goals report card</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>(Quality)</td>
<td>Number screened/</td>
<td>Number withdrawn/</td>
<td>Other population characteristics (mean scores)</td>
</tr>
<tr>
<td>--------------</td>
<td>----------</td>
<td>-----------</td>
<td>------------------</td>
<td>------------------</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Brown</td>
<td>1988</td>
<td>(Fair)</td>
<td>NR/NR/11</td>
<td>0/0/11</td>
<td>WISC-R IQ=92.91(5.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parent rating on Conners factorial rating scale(total)=0.91(0.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Teacher ratings abbreviated Conners hyperactivity Index=2.12(0.36)</td>
</tr>
<tr>
<td>Pelham</td>
<td>1991</td>
<td>(Fair)</td>
<td>NR/NR/17</td>
<td>0/0/17</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IQ=97.2(11.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DSM-III-R Structured Parent Interview:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- ADHD symptoms: 10.6(2.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- ODD symptoms: 5.7(2.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- CD symptoms: 1.9(1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abbreviated Conners Rating Scale:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Parent: 21.4(4.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Teacher: 14.9(6.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Iowa Conners Teacher Rating Scale:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- I/O: 9.5(3.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- A: 5.2(3.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Woodcock-Johnson Achievement test:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Reading: 90.2(14.9)</td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Quality</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adolescents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown</td>
<td>1988</td>
<td>Fair</td>
<td>*28 out of 36 (75%) dependent measures resulted in significant main effects for drug condition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pairwise Comparison:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo vs. 0.15mg/kg: 12/27(44%) items showed significant difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo vs. 0.30mg/kg: 14/27(52%) items showed significant difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo vs. 0.50mg/kg: 17/27(63%) items showed significant difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.15mg/kg vs. 0.30mg/kg: 5/27(18.5%) items showed significant difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.15mg/kg vs. 0.50mg/kg: 16/27(59.2%) items showed significant difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.30mg/kg vs. 0.50mg/kg: 6/27(22.2%) items showed significant difference</td>
</tr>
<tr>
<td>Pelham</td>
<td>1991</td>
<td>Fair</td>
<td>Daily behavior-modification point system: 5 out of 6 items show the effect of drug, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Teacher-recorded classroom measures: 4 out of 7 items show the effect of drug, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Teacher and counselor Conners rating scale: 2 out of 2 items show the effect of drug, p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Daily child's individual behavior and academic goals report card, 1 out of 1 items show the effect of drug, p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9 out of 17(53%) adolescent were judged to be positive responders to 0.3mg/kg methylphenidate.</td>
</tr>
</tbody>
</table>
## Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown 1988 (Fair)</td>
<td>Side Effects Rating Scale</td>
<td>number of side effect: only a significant difference was found in the comparison of 0.15mg/kg and 0.50mg/kg</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pelham 1991 (Fair)</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>
## Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varley</td>
<td>1983</td>
<td>RCT DB crossover</td>
<td>Patients with long-standing symptoms of impulsivity, short attention span, distractibility and excitability</td>
<td>100% were considered to have attention deficit disorder without hyperactivity or a conduct disorder.</td>
</tr>
<tr>
<td>Klorman</td>
<td>1986</td>
<td>RCT DB crossover</td>
<td>Scored 1.5 on the abbreviated Conners Hyperactivity Questionnaire and 1.02 on the Home Activity Scale</td>
<td>NR</td>
</tr>
<tr>
<td>Coons</td>
<td>1986</td>
<td>RCT DB crossover</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varley 1983</td>
<td>Methylphenidate 0.15mg/kg, 0.3mg/kg, bid</td>
<td>1 week/ NR</td>
<td>NR</td>
</tr>
<tr>
<td>(Fair)</td>
<td>Duration: 1 week for each condition (placebo, low dose, high dose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Timing: 8am and 12pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klorman 1986</td>
<td>Week 1: 10mg at breakfast and lunch, 5mg at 4pm</td>
<td>2-4 weeks/NR</td>
<td>NR</td>
</tr>
<tr>
<td>Coons 1986</td>
<td>Week 2: 15mg at breakfast and lunch, 10mg at 4pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Fair)</td>
<td>Week 3: 15mg at breakfast and lunch, 10mg at 4pm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varley 1983</td>
<td>Conners’ abbreviated parent/teacher questionnaire</td>
<td>Mean age=14.27 years</td>
<td>Gender: 77.3% male</td>
<td>Ethnicity: NR</td>
</tr>
<tr>
<td></td>
<td>Narrative comments regarding the subject</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Timing: daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klorman 1986</td>
<td>Abbreviated Conners Questionnaire</td>
<td>Mean age=14.80 years</td>
<td>Gender: 84.2% male</td>
<td>Ethnicity: NR</td>
</tr>
<tr>
<td>Coons 1986</td>
<td>IOWA scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sternberg Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continuous Performance Test (CPT)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varley</td>
<td>1983</td>
<td>NR/NR/22</td>
<td>0/0/22</td>
</tr>
<tr>
<td>Coons</td>
<td>1986</td>
<td>NR/NR/19</td>
<td>0/0/19</td>
</tr>
</tbody>
</table>

**Other population characteristics (mean scores)**

- **Varley 1983 (Fair)**
  - All subjects had been noted to be stimulant responders.
  - IQ mean=95.91, range 81-128

- **Klorman 1986**
  - 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)
## Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varley</td>
<td>1983</td>
<td>Dosage effects: Conners’ Parent Questionnaire, parent narrative, Coners’ Teacher Questionnaire, teacher narrative, all p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t test for correlated means (conners/ narrative)</td>
</tr>
<tr>
<td></td>
<td>(Fair)</td>
<td>Parents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- placebo vs low dose: p&lt;0.05/ p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- placebo vs high dose: p&lt;0.05/ p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- low dose vs high dose: NS/ p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teachers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- placebo vs low dose: p&lt;0.05/ p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- placebo vs high dose: p&lt;0.05/ p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- low dose vs high dose: NS/ p&lt;0.05</td>
</tr>
<tr>
<td>Klorman</td>
<td>1986</td>
<td>Parent rating (mean dose), placebo: methylphenidate</td>
</tr>
<tr>
<td>Coons</td>
<td>1986</td>
<td>Conners Scale= 1.35: 0.89, p&lt;0.03</td>
</tr>
<tr>
<td></td>
<td>(Fair)</td>
<td>I/O=1.30: 0.89, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A=1.36: 1.02, p&lt;0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teacher rating (mean dose), placebo: methylphenidate, all NS;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teacher rating (Week 3 dose), placebo: methylphenidate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conners Scale= 0.64: 0.50, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I/O=0.82: 0.64, p&lt;0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A=0.29: 0.16, p&lt;0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heart rate: rose under drug condition (100 beats/min), p&lt;0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sternberg Test: methylphenidate decreased errors and reaction time on performance, p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPT: methylphenidate reduced the rate of missed targets on performance, p&lt;0.0001;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>enhanced the index of sensitivity of detection, p&lt;0.0005; shorten P3b lantency, p&lt;0.0001</td>
</tr>
</tbody>
</table>
## Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varley</td>
<td>1983 (Fair)</td>
<td>NR</td>
<td>occasional comments regarding sleep disturbance and appetite suppression but none significant enough to warrant discontinuation of medication.</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klorman Coons</td>
<td>1986 (Fair)</td>
<td>Subjects’ Treatment Emergent Symptom Scale (STESS)</td>
<td>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, pronunciatrion, clumsiness, restlessness, fatigue, sleepiness, sleep problem, crying, irritability, unhappiness, sadness, inattention.</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
# Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith</td>
<td>1998</td>
<td>randomized, DB,</td>
<td>Adolescents</td>
<td>diagnosed with ADHD (DSM-III-R), aged 12 and up, Verbal IQ &gt;80, no conditions that precluded a trial of stimulants.</td>
<td>NR</td>
</tr>
<tr>
<td>Evans</td>
<td>2001 (Fair)</td>
<td>cross-over</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith</td>
<td>1998</td>
<td>25, 50 or 75 mg per day methylphenidate or placebo, 3 times per day, during weeks 3-8 of study.</td>
<td>2 week run in/ washout NR</td>
<td>NR</td>
</tr>
<tr>
<td>Evans</td>
<td>2001</td>
<td>(Fair)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith</td>
<td>1998</td>
<td>Timing of Assessment NR</td>
<td>n= 46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evans</td>
<td>2001</td>
<td>Omnibus test</td>
<td>mean age= 13.8 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Fair)</td>
<td>Linear trend</td>
<td>89% male</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-mg plateau</td>
<td>85% caucasian</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg plateau</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>quadratic trend</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Number screened/eligible/enrolled</td>
<td>Number withdrawn/lost to fu/analyzed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>----------</td>
<td>-----------------------------------</td>
<td>--------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith</td>
<td>1998</td>
<td>NR/49/46</td>
<td>0/0/46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evans</td>
<td>2001</td>
<td>46/46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Fair)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Other population characteristics (mean scores)

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Quality</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith</td>
<td>1998</td>
<td></td>
<td>measure: mean score at 10mg MPH vs 20mg MPH vs 30mg MPH vs placebo</td>
</tr>
<tr>
<td>Evans</td>
<td>2001</td>
<td>Fair</td>
<td>Conduct behavior frequency: 1.0 vs 0.21 vs 0.16 vs 3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Defiant behavior frequency: 11.4 vs 5.7 vs 4.3 vs 25.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Teasing peers frequency: 1.1 vs 1.0 vs 0.9 vs 2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impulsive behavior frequency: 8.3 vs 5.3 vs 4.4 vs 17.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inattention/Overactivity rating: 3.2 vs 2.7 vs 2.2 vs 4.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oppositional/defiant rating: 2.7 vs 2.3 vs 1.7 vs 3.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Success Ratio (summary of negative behaviors): 92.6 vs 94.3 vs 95.5 vs 86.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Job performance rating: 2.6 vs 2.4 vs 2.2 vs 2.8</td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith</td>
<td>1998</td>
<td>patient, parent report</td>
<td>dulled affect, social withdrawal, stomachache, loss of appetite- ns at 10 mg, but increased at 20 mg and 30 mg.</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Evans</td>
<td>2001 (Fair)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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
<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klorman</td>
<td>1990</td>
<td>RCT DB crossover</td>
<td></td>
<td>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. 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 &gt; 80 on a test administered within 6 months of referral. Subjects were in good physical health and free of all medication.</td>
<td>12(25%) Oppositional disorder plus conduct disorder 1(2.1%) alcohol use 2(4.2%) alcohol abuse 1(2.1%) marijuana abuse 1(2.1%) history of major depression 16(33.3%) past or present adjustment disorder with affective mood 5(10.4%) overanxious disorder 5(10.4%) phobia 14(29.2%) enuresis in the present or past 3(6.3%) history of encopresis</td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klorman 1990</td>
<td>weight &lt;37.5kg: week 1-- 7.5mg bid in the morning and at noon</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td>Klorman 1991</td>
<td>week 2-- 10mg bid in the morning and at noon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klorman 1992 (Fair)</td>
<td>weight between 37.5-54kg: week 3-- 10mg in the morning and at noon and 5mg at 4pm each of the above doses was incremented by 2.5mg weight &gt;54kg: each of the above doses was incremented by 5mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Duration: 1 week for each condition (baseline, placebo, drug)
Mean dosage: 35.33mg/day, or 0.64mg/kg/day
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klorman</td>
<td>1990</td>
<td>Abbreviated Conners Hyperactivity Questionnaire, weekly IOWA scale, weekly</td>
<td>Mean age=14.12 years</td>
<td>Gender: 87% male</td>
<td>Ethnicity: 96% Caucasian</td>
</tr>
<tr>
<td>Klorman</td>
<td>1991</td>
<td>Open-end questions, weekly Hyperactivity, Attention, and Aggression Scale of the Time on Task Scale (TOTs), at the end of each phase Global outcome, in the last session Continuous Performance Test (CPT)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klorman</td>
<td>1990</td>
<td>Hollingshead 4-point SES=51.33(14.29)</td>
<td>NR/NR/48</td>
<td>NR/NR/48</td>
</tr>
<tr>
<td>Klorman</td>
<td>1991</td>
<td>WISC-R full scale IQ=109.54(12.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klorman</td>
<td>1992</td>
<td>PIAT age total score=99.50(12.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Fair)</td>
<td>Home Activity Scale by parent: contemporaneous=1.35(0.94); retrospective=1.74(0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conners Hyperactivity scale: contemporaneous(parent)=1.21(0.62); retrospective(parent)=1.39(0.67); contemporaneous=1.28(0.52)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klorman</td>
<td>1990</td>
<td>Significant improvement in drug condition:</td>
</tr>
<tr>
<td>Klorman</td>
<td>1991</td>
<td>Abbreviated Conners Hyperactivity Questionnaire, by parent: p&lt;0.0005; by teacher: p&lt;0.0005</td>
</tr>
<tr>
<td>Klorman</td>
<td>1992 (Fair)</td>
<td>I/O scale, by parent: p&lt;0.002; by teacher: p&lt;0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aggression scale, by parent: p&lt;0.006; by teacher: p&lt;0.0002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>valence of comments, by parent: p&lt;0.007; by teacher: p&lt;0.0001</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klorman</td>
<td>1990</td>
<td>Subjects’ Treatment Emergent Symptom Scale (STESS)</td>
<td>Appetite loss: by parent, 0.05; by patient, p&lt;0.001&lt;br&gt;Increased thirst: NS&lt;br&gt;Dry mouth: by parent, NS; by patient, p&lt;0.1&lt;br&gt;Stomachaches: NS&lt;br&gt;Nausea: NS&lt;br&gt;Headaches: NS&lt;br&gt;Sleep problem: NS&lt;br&gt;Shakiness: by parent, NS; by patient, p&lt;0.1&lt;br&gt;Crying: NS&lt;br&gt;Anger: NS&lt;br&gt;Unhappiness: NS&lt;br&gt;Sadness: NS</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bostic 2000</td>
<td>pemoline dosed twice daily (morning and after school), week 1: increased 1mg/kg/day week 2: increased 2mg/kg/day week 3: increased 3mg/kg/day or placebo.</td>
<td>10 week study period. NR Washout required of at least 2 weeks of all psychotropics before study. 2 treatment periods lasting 4 weeks, separated by 2 week washout periods.</td>
<td>NR</td>
</tr>
</tbody>
</table>

Mean dose at week 3= 150.6 mg
**Evidence Table 1. Placebo-controlled trials in preschool children and adolescents**

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bostic 2000 (Fair)</td>
<td>DSM-IV derived ADHD scale, at end of each treatment arm.</td>
<td>mean age: 14 yrs</td>
<td>males: 86%</td>
<td>caucasian: 90%</td>
</tr>
</tbody>
</table>
Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/ eligible/ enrolled</th>
<th>Number withdrawn/ lost to follow/ analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bostic 2000</td>
<td>Fair</td>
<td>previous diagnosis of ADHD with meds: 43%</td>
<td>32 screened/ 22 eligible/ 21 enrolled</td>
<td>0 withdrawn/ 4 lost to follow/ 21 analyzed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>previously treated with at least 1 stimulant: 7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>previously treated with 2 stimulants: 23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>previously treated with tricyclic antidepressants: 9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>moderate ADHD: 57%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>severe ADHD: 14%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>(Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bostic</td>
<td>2000</td>
<td>(Fair)</td>
<td><strong>ADHD Rating Scale</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>symptom cluster: mean score pemoline vs mean score placebo; p-value</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity (DSM-IV): 9.5 vs 12.68; 0.040</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulty remaining seated: 1.15 vs 1.89; 0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>is fidgety: 1.80 vs 2.53; 0.028</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>has difficulty playing quietly: 1.40 vs 1.95; 0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>talks excessively: 1.80 vs 2.05; 0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>feels on the go: 1.75 vs 2.00; 0.673</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inattentiveness (DSM-IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>shifts activities: 1.70 vs 2.16; 0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulty sustaining attention: 1.75 vs 2.47; 0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulty following directions: 1.75 vs 2.26; 0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>loses things: 1.15 vs 1.74; 0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>easily distracted: 1.90 vs 2.84; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>doesn't listen: 1.75 vs 2.26; 0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>makes careless mistakes: 1.65 vs 2.37; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulty organizing: 1.75 vs 2.42; 0.0065</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>avoids mental tasks: 1.70 vs 2.42; 0.009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>forgetful: 1.80 vs 2.26; 0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impulsivity (DSM-IV)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>interrupts: 4.00 vs 5.79; &lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>blurts out: 1.45 vs 2.10; 0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulty waiting turn: 1.15 vs 1.63; 0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>acts before thinking: 1.65 vs 2.42; 0.002</td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bostic</td>
<td>2000 (Fair)</td>
<td>patient report</td>
<td>Adverse event: % pemoline vs % placebo; p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>insomnia: 62% vs 5%; p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>loss of appetite: 38% vs 10%; p=0.014</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>headache: 29% vs 33%; p=0.763</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>gastrointestinal pain: 20% vs 10%; p=0.414</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>agitation: 10% vs 0%; p=0.157</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>sedation: 0% vs 5%; p=0.317</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>increased appetite: 5% vs 0%; p=0.317</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hearing loss: 5% vs 0%; p=0.317</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmann 2001</td>
<td>(Fair)</td>
<td>randomized, DB, cross-over</td>
<td>children aged 5-15 diagnosed with ADHD (DSM-III), ACTeRS Attention score at or below 25th percentile, ACTeRS Hyperactivity Score at or below 25th percentile, CTRS-28 Inattention/Passivity Scale 2 or more sd above mean, CTRS-28 Hyperactivity Index 2 or more sd above mean, CPRS-48 Hyperactivity Index 2 or more sd above mean</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmann 2001</td>
<td>0.3 mg/kg and 0.5 mg/kg doses, and placebo, 3 times per day, in 7 day cycles, in 2 weeks trials.</td>
<td>run-in NR, no washouts due to short half-life of ritalin</td>
<td>NR</td>
</tr>
</tbody>
</table>
**Evidence Table 1. Placebo-controlled trials in preschool children and adolescents**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmann 2001</td>
<td>Fair</td>
<td>Weekly completion of (BSEQ) Barkley Side Effects Questionnaire, by parents.</td>
<td>n=79</td>
<td>ethnicity NR</td>
<td>ages 10-15y, 79.7% males</td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmann 2001</td>
<td>Fair</td>
<td>NR</td>
<td>NR/NR/NR</td>
<td>NR/NR/79</td>
</tr>
</tbody>
</table>

NR: Not reported.
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Barkley Side Effects Questionnaire Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmann</td>
<td>2001</td>
<td><strong>Ritalin vs placebo, p value</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Insomnia:</strong> 51.3 vs 26.3, <em>p</em>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Decreased appetite:</strong> 61.8 vs 25.0, <em>p</em>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Stomachache:</strong> 36.8 vs 14.5, <em>p</em>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Headache:</strong> 38.7 vs 22.7, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Dizziness:</strong> 10.7 vs 1.3, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Daydreaming:</strong> 42.7 vs 52.0, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Irritability:</strong> 62.2 vs 80.3, <em>p</em>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Anxiety:</strong> 50.7 vs 64.0, NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Nailbiting:</strong> 26.7 vs 36.0, NS</td>
</tr>
</tbody>
</table>
### Evidence Table 1. Placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th>Author</th>
<th>Year/Quality</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmann</td>
<td>2001/Fair</td>
<td>patient/parent report</td>
<td>&quot;dazed&quot;, with rapid heartbeat and difficulty breathing: n=1</td>
<td>4 withdrawals, all due to adverse events.</td>
<td>the study includes the largest group of girls with ADHD reported in the literature (n=45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&quot;zombie&quot;: n=1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>stomachache, headache, decreased appetite and insomnia: n=1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>decreased appetite and sleep problems: n=1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------</td>
<td>---------------------------------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Preschool children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schleifer 1975</td>
<td>NR</td>
<td>NR</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barkley 1988</td>
<td>NR</td>
<td>NR</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musten 1997 Firestone 1998</td>
<td>NR</td>
<td>Yes</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conners 1975</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

### External Validity

<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schleifer 1975</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/28</td>
<td>NR</td>
</tr>
<tr>
<td>Barkley 1988</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/27</td>
<td>NR</td>
</tr>
<tr>
<td>Musten 1997 Firestone 1998</td>
<td>No; Analysis excluded 10 patients (24%) - 4 &quot;withdrew&quot; and 6 &quot;did not have completed assessment protocols&quot;</td>
<td>No</td>
<td>Fair</td>
<td>109(43 refused, 64 agreed)/54/41</td>
<td>NR</td>
</tr>
<tr>
<td>Conners 1975</td>
<td>No; different numbers of patients were excluded from analyses at each time point due to &quot;missing data&quot;</td>
<td>No</td>
<td>Poor</td>
<td>NR/66/59</td>
<td>Marked anxiety, tension, or agitation thought to result from current psychological stress in the home; hypersensitivity to MPH; glaucoma; epilepsy; severe organic brain damage; or need during therapy for any other psychotropic drugs; pressor agents, MAO inhibitors, phenybutazone, or coumarin-type anti-coagulants</td>
</tr>
</tbody>
</table>
## Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

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

**Note:** For the purpose of this table, run-in and washout periods are not applicable as the trials are focused on preschool children.
## Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adolescents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown 1988</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Pelham 1991</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Varley 1983</td>
<td></td>
<td>Yes</td>
<td>NR</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Klorman 1986</td>
<td>Coons 1986</td>
<td>NR</td>
<td>NR</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Smith 1998</td>
<td>Evans 2001</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
</tbody>
</table>

Pharmacologic Treatments for ADHD
### Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

*External Validity*

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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>** Adolescents**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown 1988</td>
<td>NR/NR</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Pelham 1991</td>
<td>NR/NR</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Varley 1983</td>
<td>NR/NR</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Klorman 1986, Coons 1986</td>
<td>NR/Yes (see exclusion criteria)</td>
<td>No</td>
<td>Yes</td>
<td>NIMH Grants MH 32103 and MH38118</td>
</tr>
<tr>
<td>Smith 1998, Evans 2001</td>
<td>Run-in: NR Wash-out: 2 weeks prior to randomization</td>
<td>No</td>
<td>Yes</td>
<td>National Institute on Drug Abuse, NIMH, National Institute on Alcohol Abuse and Alcoholism, and the National Institute of Child Health and Human Development</td>
</tr>
</tbody>
</table>
## Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

### Internal Validity

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Klorman 1990</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Klorman 1991</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Klorman 1992</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td>Bostic 2000</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Ahmann 2001</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 2. Quality of placebo-controlled trials in preschool children and adolescents

*External Validity*

<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klorman 1990</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/48</td>
<td>CNS involvement, childhood autism, psychosis, physical handicaps, and uncorrected visual or auditory problems, mental deficiency</td>
</tr>
<tr>
<td>Klorman 1991</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klorman 1992</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bostic 2000</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>32/21/21</td>
<td>Clinically significant medical conditions or abnormal baseline laboratory liver function tests, mental retardation, organic brain disorders, unstable psychiatric conditions, bipolar disorder, psychosis, drug or alcohol abuse of dependence within the prior 6 months, or active pregnancy or nursing.</td>
</tr>
<tr>
<td>Ahmann 2001</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/234</td>
<td>History of seizures, mental retardation, Tourette's syndrome, or other significant neurologic history</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Run-in/Washout</td>
<td>Class naïve patients only</td>
<td>Control group standard of care</td>
<td>Funding</td>
<td>Relevance</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>--------------------------</td>
<td>--------------------------------</td>
<td>---------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Klorman 1990</td>
<td>NR</td>
<td>95.8% treatment naïve</td>
<td>Yes</td>
<td>NIMH grant MH38118</td>
<td>NR</td>
</tr>
<tr>
<td>Klorman 1991</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Klorman 1992</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Bostic 2000</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
<td>Eli Lilly, Inc.</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Patients on psychotropics were required to washout at least 2 weeks before the beginning of the study; treatment periods were separated by 2-week washout period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahmann 2001</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
<td>Marshfield Clinic grants 0844-01-87 and 0844-01-90</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine vs. methylphenidate IR</td>
<td></td>
<td>Diagnosis of Minimal Brain Dysfunction with such signs 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 &quot;placebo washout&quot; to be maintained without active drug</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine vs. methylphenidate IR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arnold 1978</td>
<td>NR</td>
<td>Days 1/2/3+: Dextroamphetamine: 5/10/15 mg Methylphenidate: 10/20/30 mg</td>
<td>2-week placebo washout</td>
<td></td>
</tr>
<tr>
<td>Huestis 1975</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>3 weeks, then crossover</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice daily: morning and noon</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine vs.</td>
<td>Parents' Symptom Checklist (Arnold and Smeltzer) Conners Teachers' Behavior Checklist; Davids' Hyperkinetic Rating</td>
<td>Mean age=8</td>
<td>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</td>
</tr>
<tr>
<td>methylphenidate IR</td>
<td>Scale (completed by both parents and teachers); target symptom assessment/quantification using 9-point scale (1=excellent, 5=no change from placebo washout; 9=disastrous)</td>
<td>75.9% male</td>
<td>Race nr</td>
</tr>
<tr>
<td>Arnold 1978</td>
<td></td>
<td>Race nr</td>
<td></td>
</tr>
<tr>
<td>Huestis 1975</td>
<td></td>
<td>Race nr</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Race nr</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine vs. methylphenidate IR</td>
<td></td>
<td></td>
<td>Mean changes on (p=NS for all):</td>
</tr>
<tr>
<td>Arnold 1978</td>
<td>NR</td>
<td>NR</td>
<td>Conners' school behavior checklist by teachers: -21.26 vs -17.97</td>
</tr>
<tr>
<td>Huestis 1975</td>
<td>NR</td>
<td>NR</td>
<td>Sum of first 6 items on Davids' Hyperkinetic Rating Scale by teacher: -6.65 vs -5.89</td>
</tr>
<tr>
<td>Fair</td>
<td>29</td>
<td>29</td>
<td>Item 7 (poor schoolwork) on Davids' Hyperkinetic Rating Scale by teachers: -0.69 vs -0.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>First six items on Davids' Hyperkinetic Rating Scale by parents: -5.45 vs -5.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Problem checklist by parents: -43.1 vs -37.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Psychiatrists' ratings of parent-assessed target symptoms: -1.87 vs -1.62</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine vs. methylphenidate IR</td>
<td>Mean side effects reported by parents on checklist (1=not at all; 4=very much)</td>
<td>Poor appetite: -0.45 vs 0.35</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Arnold 1978</td>
<td></td>
<td>Awake at night: 0.07 vs -0.03</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Huestis 1975</td>
<td></td>
<td>Headaches: -0.27 vs -0.27</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Tummyaches: -0.41 vs -0.31</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side effects of drug: 0.25 vs 0.25</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Mean change in weight (kg): -1.32 vs -0.92; p=NS
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron</td>
<td>RCT with crossover</td>
<td>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: &quot;never or rarely,&quot; (0); &quot;sometimes,&quot; (1); &quot;often,&quot; (2); and &quot;very often,&quot; (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.</td>
</tr>
<tr>
<td>1997</td>
<td>Single center</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron 1997</td>
<td>NR</td>
<td>Dextroamphetamine 0.15mg/kg Methylphenidate 0.3 mg/kg Both rounded off to the nearest capsule size</td>
<td>24-hour washout</td>
<td>NR</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>x 2 weeks then crossover</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron 1997</td>
<td>Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III), 28-item Conners’ Teacher Rating Scale-Revised (CTRS-R), 48-item Conners’ Parent Rating Scale-Revised (CPRS-R), Continuous Performance Test (CPT), Child Behavior Checklist (CBCL)</td>
<td>8.7 years</td>
<td>NR</td>
<td>NR</td>
<td>ADHD-mixed type=101(81.8%) ADHD-predominantly inattentive=22(17.6%) ADHD-predominantly hyperactive/impulsive=2(1.6%) Mean IQ=98.9</td>
</tr>
<tr>
<td>Fair Australia</td>
<td>Continuous Performance Test (CPT), Child Behavior Checklist (CBCL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron 1997</td>
<td>NR</td>
<td>NR</td>
<td>% subjects rated by their parents as improved overall compared with their usual selves: 86 (68.8%) vs 90 (72%); p=NS</td>
</tr>
<tr>
<td>Australia</td>
<td>125</td>
<td>125</td>
<td>(CTRS-R and CPRS-R data generally corroborated with these proportions of global response to the two stimulants)</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Method of adverse effects assessment</td>
<td>Adverse Effects Reported</td>
<td>Total withdrawals; withdrawals due to adverse events</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------</td>
<td>--------------------------</td>
<td>---------------------------------------------</td>
</tr>
</tbody>
</table>
| Efron 1997 Australia | Side Effects Rating Scale (SERS) | Trouble sleeping: 88(70%) vs 79(64%), p=NS  
Poor appetite: 74(59%) vs 69(56%), p=NS  
Irritable: 102(82%) vs 100(80%), p=NS  
Proneness to crying: 95(76%) vs 89(71%), p=NS  
Anxiousness: 85(68%) vs 76(61%), p=NS  
Sadness/unhappiness: 74(59%) vs 69(56%), p=NS  
Headaches: 38(30%) vs 30(24%), p=NS  
Stomachaches: 50(40%) vs 40(32%), p=NS  
Nightmares: 35(28%) vs 26(21%), p=NS  
Daydreams: 78(62%) vs 77(62%), p=NS  
Talking little with others: 37(30%) vs 35(28%), p=NS  
Uninterested in others: 43(34%) vs 39(31%), p=NS  
Drowsiness: 23(18%) vs 22(18%), p=NS  
Biting fingernails: 50(40%) 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  
Severe: 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%) |
# Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron</td>
<td>RCT with crossover</td>
<td>Single center</td>
<td>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: &quot;never or rarely,&quot; (0); &quot;sometimes,&quot; (1); &quot;often,&quot; (2); and &quot;very often,&quot; (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.</td>
</tr>
<tr>
<td>Efron</td>
<td>RCT with crossover</td>
<td>Single center</td>
<td>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</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron</td>
<td>NR</td>
<td>Dextroamphetamine 0.15mg/kg&lt;br&gt;Methylphenidate 0.3 mg/kg&lt;br&gt;Both rounded off to the nearest capsule size</td>
<td>24-hour washout</td>
<td>NR</td>
</tr>
<tr>
<td>1998 Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>x 2 weeks then crossover</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elia</td>
<td>Comorbid conduct disorder: 7 (22.6%)&lt;br&gt;Comorbid oppositional disorder: 6 (19.4%)&lt;br&gt;Comorbid specific developmental disorders: 9 (29%)</td>
<td>Weeks 1, 2, and 3 for children &lt; 30 kg/&lt;br&gt;Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg&lt;br&gt;Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg</td>
<td>≥ 3 weeks washout</td>
<td>NR</td>
</tr>
<tr>
<td>1990 United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>3 weeks then crossover&lt;br&gt;Twice daily at 9 am and 1 pm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron</td>
<td>Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III), 28-item Conners’ Teacher Rating Scale-Revised (CTRS-R), Parent Rating Scale-Revised (CPRS-R), Continuous Performance Test (CPT), Child Behavior Checklist (CBCL)</td>
<td>Mean age= 9.3 years</td>
<td>91.2% male</td>
<td>Race nr</td>
<td>ADHD-Mixed type=84(82.4%)                         ADHD-predominantly inattentive=17(16.7%)</td>
</tr>
<tr>
<td>1998</td>
<td>Study subjects/parents were also asked to rate how they felt whilst taking each medication, compared to their usual self, at the completion of each cycle using a dichotomised 5-point scale (Nonresponse='worse than usual', 'much worse than usual' or about the same as usual'; Response='better than usual' or 'much better than usual' Children also asked to rate &quot;How helpful was the medication?&quot; on a 5-point scale, from 'very helpful to 'not at all helpful'</td>
<td></td>
<td></td>
<td></td>
<td>ADHD-predominantly hyperactive/impulsive=1(1%)</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
<td>Mean IQ=98.8</td>
<td></td>
<td></td>
<td>Learning disability for reading=30(27.3%)</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Learning disorder for spelling=36(32.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elia</td>
<td>CTRS</td>
<td>Mean age=8.5 years</td>
<td></td>
<td></td>
<td>Mean Full Scale WISC-R IQ=102</td>
</tr>
<tr>
<td>1990</td>
<td>CPRS</td>
<td>years</td>
<td></td>
<td></td>
<td>Mean CTRS factor I (conduct)/factor IV (hyperactivity): 1.3/2.6</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td>100% male</td>
<td></td>
<td></td>
<td>Mean CPRS factor I (conduct)/factor IV (hyperactivity): 1.6/2.4</td>
</tr>
<tr>
<td>Fair</td>
<td>CPT</td>
<td>Race nr</td>
<td></td>
<td></td>
<td>Stimulant naïve: 18 (37.5%)</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron 1998</td>
<td>NR</td>
<td>NR</td>
<td>Dextroamphetamine versus methylphenidate:</td>
</tr>
<tr>
<td>Australia</td>
<td>102</td>
<td>102</td>
<td>Child's rating: &quot;When I took this medication I felt:&quot; (cases/%)</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td>Much worse than usual: 6/5.9 vs 5/4.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Worse than usual: 13/12.9 vs 8/7.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>About the same as usual: 26/25.7 vs 25/24.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Better than usual: 23/22.8 vs 35/34.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Much better than usual: 33/32.7 vs 29/28.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child's rating: &quot;How helpful was the medication?&quot; (cases/%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Very helpful: 39/38.6 vs 46/45.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A bit helpful: 25/24.8 vs 29/28.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not sure: 27/26.7 vs 15/14.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not very helpful: 5/5 vs 4/3.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not at all helpful: 5/5 vs 8/7.8</td>
</tr>
<tr>
<td>Elia 1990</td>
<td>NR</td>
<td>NR</td>
<td>dextroamphetamine = methylphenidate on all measures (limited data provided in graph format)</td>
</tr>
<tr>
<td>United States</td>
<td>31</td>
<td>NR</td>
<td>Estimated from graphs (dextroamphetamine vs methylphenidate)</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td>Mean changes in (all p=NS):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CGI: +2.5 vs +2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPT (# correct): +9 vs +10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CTRS Factor I: -0.4 vs -0.4; CTRS Factor IV: -0.8 vs -0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPRS Factor I: -0.7 vs -0.6; CPRS Factor IV: -1.2 vs -1</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron 1998 Australia</td>
<td>SERS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Elia 1990 United States</td>
<td>STESS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia 1991</td>
<td>RCT with crossover</td>
<td>Single center</td>
<td>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).</td>
</tr>
<tr>
<td>Schmidt 1994</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia 1991</td>
<td>Comorbid conduct disorder: 10 (20.8%)</td>
<td>Weeks 1, 2, and 3 for children &lt; 30 kg/ &gt; 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Schmidt 1994</td>
<td>Comorbid oppositional disorder: 12 (25%)</td>
<td>3 weeks then crossover</td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>Comorbid specific developmental disorders: 11 (22.9%)</td>
<td>Twice daily at 9 am and 1 pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>Comorbid dysthymic disorder: 1 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia 1991</td>
<td>ABTRS</td>
<td>Mean age=8.6 years</td>
<td></td>
<td></td>
<td>Mean Full Scale WISC-R IQ=105.6</td>
</tr>
<tr>
<td>Schmidt 1994</td>
<td>CTRS</td>
<td>Mean CTRS factor I (conduct) - teacher/parent rating: 1.3/1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>CPRS</td>
<td>Mean CTRS factor IV (hyperactivity) - teacher/parent rating: 2.6/2.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>CPQ</td>
<td>Stimulant naïve: 18 (37.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CGI</td>
<td></td>
<td>100% male</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C-GAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Palwin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Truncal motor activity monitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia 1991</td>
<td>NR</td>
<td>NR</td>
<td>dextroamphetamine=methylphenidate on all measures (limited data provided in graph format)</td>
</tr>
<tr>
<td>Schmidt 1994</td>
<td>NR</td>
<td>NR</td>
<td>Estimated from graphs (dextroamphetamine vs methylphenidate)</td>
</tr>
<tr>
<td>United States</td>
<td>48</td>
<td>NR</td>
<td>Mean changes in (all p=NS):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CGI: 2.3 vs 2.4; GAS: 5 vs 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>39-item Conners Factor I (conduct): -0.41 vs -0.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48-item Conners Factor I (conduct): -0.5 vs -0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPT (# omission errors): -11 vs -11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>39-item Conners Factor IV (hyperactivity): -0.9 vs -1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>48-item Conners Factor IV (hyperactivity): -1.2 vs -1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPT (# commission errors): -13 vs -14</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia 1991</td>
<td>STESS</td>
<td>dextroamphetamine vs methylphenidate (% patients with mild/moderate/severe severity scores on STESS) (all p=NS)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Schmidt 1994</td>
<td>CPRS</td>
<td>Decreased appetite (n=48): 40/42/13 vs 40/35/10</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td>Sleep difficulties (n=48): 31/40/10 vs 40/31/8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Overly meticulous (n=33): 18/12/6 vs 30/3/0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not happy (n=48): 25/33/4 vs 27/35/6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>dextroamphetamine vs methylphenidate (% patients with mild/moderate/severe severity scores on CPRS) (p=NS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nervous habits and mannerisms: 35/9/0 vs 26/21/3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casellanos 1997</td>
<td>RCT with crossover Single center</td>
<td>(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</td>
</tr>
<tr>
<td>United States</td>
<td>Single center</td>
<td></td>
</tr>
<tr>
<td>Subgroup of Elia 1991</td>
<td></td>
<td>Tourette's syndrome</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casellanos 1997</td>
<td>Conduct disorder=1(5%)</td>
<td>Group 1 (n=12), Low-medium-high</td>
<td>≥ 4 weeks washout</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>United States</td>
<td>Oppositional defiant disorder=6(30%)</td>
<td>Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup of Elia 1991</td>
<td>Reading disorder=1(5%)</td>
<td>Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overanxious disorder=1(5%)</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obsessive-compulsive disorder=2(10%)</td>
<td>Group 2 (n=6), Low-medium-medium</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enuresis=4(20%)</td>
<td>Dextroamphetamine 10, 25, and 25 mg/15, 30, and 30 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylphenidate 25, 40 and 40 mg/30, 50 and 50 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group 3 (n=4), Low-high-high</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dextroamphetamine 10, 40, and 40 mg/15, 45, and 45 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylphenidate 25, 70 and 70 mg/30, 90 and 900 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 weeks then crossover</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice daily at 9 am and 1 pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individualized curriculum and instruction provided from 9 am to 12:30 pm in a highly structured classroom.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>This included a positive reinforcement management program using play money. Children were paid for appropriate behavior and fined for inappropriate behavior.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casellanos 1997</td>
<td>CTRS Historical and Examiner’s Ratings from the Unified Rating Scale provided by the Tourette Syndrome Association (modified from Yale Global Tic Severity Scale)</td>
<td>Mean age=9.4</td>
<td>Gender nr</td>
<td>80% white</td>
<td>WISC-R Full Scale IQ=98.8</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WISC-R Verbal=102</td>
</tr>
<tr>
<td>Subgroup of Elia 1991</td>
<td>Scale)</td>
<td></td>
<td></td>
<td></td>
<td>WISC-R Performance=95.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yale Global Tic Severity Scale (0-104)=37.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CTRS Conduct/Hyperactivity factors=0.59/1.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C-GAS=42.6</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casellanos 1997</td>
<td>NR</td>
<td># withdrawn: Group 1=2(9.1%)</td>
<td>Tic severity</td>
</tr>
<tr>
<td>United States</td>
<td>NR</td>
<td>2=nr, Group 3=n4/lost to fu nr</td>
<td>Dextroamphetamine had greater severity than placebo (+25%), p&lt;0.05</td>
</tr>
<tr>
<td>Subgroup of Elia 1991</td>
<td>Enrolled: Group 1=22, Group 2=6, Group 3=4</td>
<td>2=nr, Group 3=nr</td>
<td>Methylphenidate severity indistinguishable from placebo (-4%), p=NS</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casellanos 1997 United States</td>
<td>NR</td>
<td># cases with dextroamphetamine vs methylphenidate (denominator unclear)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Subgroup of Elia 1991</td>
<td></td>
<td>Marked appetite suppression with transient weight loss: 4 vs 3 Initial insomnia: 10 vs 2</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transient obsessive-compulsive symptoms: 1 vs 5</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia 1993</td>
<td>RCT with crossover</td>
<td>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 &gt; 80.</td>
</tr>
<tr>
<td>Fair</td>
<td>Single center</td>
<td></td>
</tr>
<tr>
<td>Kauffman 1981</td>
<td>RCT with crossover</td>
<td>Children diagnosed as &quot;hyperactive,&quot; according to a set of predetermined clinical criteria</td>
</tr>
<tr>
<td>Fair</td>
<td>Single center</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia 1993</td>
<td>Comorbid conduct disorder: 6 (18.2%)</td>
<td>Weeks 1, 2, and 3 for children &lt; 30 kg/ &gt; 30 kg: Dextroamphetamine 10, 25, and 40 mg/15, 30, and 45 mg Methylphenidate 25, 40 and 70 mg/30, 50 and 90 mg</td>
<td>≥ 3 weeks washout</td>
<td>NR</td>
</tr>
<tr>
<td>United States</td>
<td>Comorbid oppositional disorder: 7 (21.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>Comorbid developmental disorders: 9 (27.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kauffman 1981</td>
<td>NR</td>
<td>Dextroamphetamine 10-60 mg Methylphenidate 5-30 mg Placebo</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Twice daily: morning and noon 6 weeks, then crossover</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Individualized curriculum and instruction provided from 9 am to 12:30 pm in a highly structured classroom. This included a positive reinforcement management program using play money. Children were paid for appropriate behavior and fined for inappropriate behavior.
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia</td>
<td>Specific Skill Series Reading (Barnell Loft, Ltd)</td>
<td>Mean age= 9.3 years</td>
<td>Gender NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>Developing Key Concepts in Math (Barnell Loft, Ltd)ABTRS</td>
<td></td>
<td></td>
<td></td>
<td>Mean Full Scale WISC-R IQ=108.8</td>
</tr>
<tr>
<td>United States</td>
<td>CTQ-R</td>
<td></td>
<td></td>
<td></td>
<td>Mean CTQ-R factor I (conduct)=1.16</td>
</tr>
<tr>
<td>Fair</td>
<td>CGI</td>
<td></td>
<td></td>
<td></td>
<td>Mean CTQ-R factor IV (hyperactivity)=2.49</td>
</tr>
<tr>
<td></td>
<td>C-GAS</td>
<td></td>
<td></td>
<td></td>
<td>Mean CPQ-R factor I (conduct)=1.49</td>
</tr>
<tr>
<td></td>
<td>Rosvold's A-X Continuous Performance Task</td>
<td></td>
<td></td>
<td></td>
<td>Mean CPQ-R factor IV (hyperactivity)=2.26</td>
</tr>
<tr>
<td>Kauffman</td>
<td>Urine sample</td>
<td>Mean age nr</td>
<td>100% male</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>1981</td>
<td>Returned capsules were recorded</td>
<td></td>
<td></td>
<td></td>
<td>100% white</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pharmacologic Treatments for ADHD
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
</table>
| Elia 1993 United States | NR/33 | NR/NR/33 | Combined Reading Scores  
Percent correct  
Dextroamphetamine vs Placebo=89.5 vs 86.1; p<0.01  
Methylphenidate vs Placebo=89.7 vs 86.1; p<0.01  
Mean number of attempts  
Dextroamphetamine vs Placebo=11.4 vs 9.5; p<0.01  
Methylphenidate vs Placebo=10.6 vs 9.5; p<0.01  
Dextroamphetamine vs Methylphenidate: p<0.05 |
| Fair        | NR/12 | NR/NR/12 | Combined Arithmetic Scores  
Percent correct  
Dextroamphetamine vs Placebo=97.1 vs 94.0; p<0.05  
Methylphenidate vs Placebo=96.2 vs 94.0; p=NS  
Mean number of attempts  
Dextroamphetamine vs Placebo=38.3 vs 30.5; p<0.01  
Methylphenidate vs Placebo=39.2 vs 30.5; p<0.05 |
| Kauffmann 1981 | NR/12 | NR/NR/12 | % patients with positive urinalysis: 60 vs 67; p=NS  
% of patient-weeks with missed doses recorded: 18 vs 13; p=NS |
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia 1993</td>
<td>STESS</td>
<td>% patients (dextroamphetamine vs methylphenidate)</td>
<td>Withdrawals due to adverse events: 0 vs 0</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td>Decreased appetite: 43 vs 46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Difficult with sleeping: 42 vs 36</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Overly meticulous behavior: 24 and 21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seemed unhappy: 12 vs 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transient tics or other nervous mannerisms: 36 vs 39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kauffman 1981</td>
<td>Side effects checklist (not specified)</td>
<td>Anorexia (incidence/patient-week): 0.32 vs 0.26; both significantly different from placebo</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Insomnia (incidence/patient-week): 0.20 vs 0.36; only methylphenidate significantly different from placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean change in weight (kg): -0.86 vs +0.11; significant difference bewteen active drugs (p nr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean change in height (cm): +0.4 vs +0.4; neither significantly different from placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross 1976</td>
<td>RCT with crossover Single center</td>
<td>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</td>
</tr>
<tr>
<td>Study</td>
<td>Comorbidity</td>
<td>Interventions and total daily dose</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Gross</td>
<td>NR</td>
<td>Age group 3-4/5-6/7-8/9-11/12-14:</td>
</tr>
<tr>
<td>1976</td>
<td>Poor</td>
<td>Dextroamphetamine: 2.5/4.5/7.25/10/11.25 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylphenidate: 4.5/10/15/20/22.5 mg</td>
</tr>
</tbody>
</table>
**Evidence Table 3. Head to Head trials in children with ADHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross 1976</td>
<td>Parents asked to rate each week in terms of improvements in target symptoms and get similar ratings from the child's teacher(s): -2=much worse, -1=slightly worse, 0=no really significant change, +1=slightly improved, +2=definite improvement but symptoms still pronounced, +3=considerably improved, +4=excellent improvement but some symptoms still present to a significant degree, and +5=outstanding improvement with few residual symptoms</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross</td>
<td>NR</td>
<td>2 (4%) withdrawn/lost to fu nr/analyzed: dextroamphetamine=48 vs methylphenidate=46</td>
<td>Average improvement: 2.3 vs 2.2; p=NS</td>
</tr>
<tr>
<td>1976</td>
<td>NR</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

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

*NR = Not reported*
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borcherding 1990</td>
<td>RCT with crossover Single center</td>
<td>DSM-III diagnosis of Attention Deficit Disorder with Hyperactivity (ADDH); medically healthy; WISC-R full scale IQ score &gt; 80; score 2 SDs or above their age norms on Factor 4 (hyperactivity) of the CTRS</td>
</tr>
<tr>
<td>Study</td>
<td>Comorbidity</td>
<td>Interventions and total daily dose</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Borcherding</td>
<td>NR</td>
<td>Mean dosages for weeks 1/2/3:</td>
</tr>
<tr>
<td>1990</td>
<td>Poor</td>
<td>Dexamethylphenidate 0.2/0.5/0.7 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylphenidate 0.5/0.8/1.3 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 weeks then crossover</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice daily: 9 a.m. and 1 p.m.</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borcherding 1990</td>
<td>Efficacy nr</td>
<td>Mean age=8.6 years</td>
<td>100% male</td>
<td>71.7% white, 2.2% black, 6.5% hispanic/asiatic</td>
<td>WISC-R Full Scale IQ=106.1 Mean CTRS for Factor 4 (hyperactivity)/Factor 1 (conduct): 2.5/1.2 28.3% stimulant naïve</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Evidence Table 3. Head to Head trials in children with ADHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/ eligible/enrolled</th>
<th>Withdrawn/ lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borcherding</td>
<td>NR</td>
<td>1 (2.2%)</td>
<td>Efficacy nr</td>
</tr>
<tr>
<td>1990</td>
<td>NR</td>
<td>withdrawn/lost to fu</td>
<td>nr/# analyzed ranged by outcome</td>
</tr>
<tr>
<td>Poor</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Method of adverse effects assessment</td>
<td>Adverse Effects Reported</td>
<td>Total withdrawals; withdrawals due to adverse events</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>Borcherding</td>
<td>STESS (rated by physician/child's parents) + 4 items (orofacial, stereotypic, other tics, tremor)</td>
<td>Abnormal movements</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>1990 Poor</td>
<td>3 items from CPRS (nervous habits/mannerisms, compulsive acts, obsessive thinking)</td>
<td>Abnormal movements &quot;NOTED&quot;: 34/45 (76%) overall Abnormal movements &quot;OBSERVED&quot;: 27/34 (79%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td></td>
<td>STESS items (mean scores)</td>
<td>Compulsive behaviors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Does things over &amp; over a certain number of times before they seem quite right (n=38): 0.4 vs 0.4; both &gt; placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meticulous; pays close attention to detail: 0.4 vs 0.3; both &gt; placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overly neat and clean: 0.2 vs 0.1; only dextroamphetamine &gt; placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Has trouble making up his mind: 0.4 vs 0.5; methylphenidate &gt; placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jerks/twitches or unusual movements: 0.2 vs 0.2; both = placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPRS items (mean scores) (all &quot;both &gt; placebo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Compulsive acts: 1.7 vs 1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nervous habits &amp; mannerisms: 1.8 vs 1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obsessive thinking: 2.0 vs 2.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharp 1999</td>
<td>RCT with crossover</td>
<td>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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharp 1999</td>
<td>NR</td>
<td>Mean doses for weeks 1, 2, and 3:</td>
<td>3-week washout</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dextroamphetamine 0.23, 0.43, and 0.64 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylphenidate 0.45, 0.85 and 1.28 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice daily: breakfast and lunch</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 weeks, then crossover</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age Gender Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharp</td>
<td>WISC-RR, Woodcock-Johnson Achievement Battery, Conners Hyperactivity and Conduct factors, CBCL, TRF, C-GAS, CGI-SI, CPT</td>
<td>n=42 (includes 10 girls from another, unpublished trial of sustained release dextroamphetamine vs adderall)</td>
<td>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</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>n=42 (includes 10 girls from another, unpublished pilot trial of sustained release dextroamphetamine vs adderall)</td>
<td>Mean age=8.9  100% female  67% white, 19% black, 14% latina</td>
</tr>
</tbody>
</table>

(n=42 includes 10 girls from another, unpublished pilot trial of sustained release dextroamphetamine vs adderall)
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/ eligible/ enrolled</th>
<th>Withdrawn/ lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharp 1999</td>
<td>150/NR/32</td>
<td>1 (3.1%) withdrawn/lost to fu</td>
<td>% patients with CGI--GI ratings of &quot;very much improved&quot; or &quot;much improved&quot;: 85% vs 83%; p=NS</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharp 1999</td>
<td>NR</td>
<td>Mean change in body weight (kg)</td>
<td>1 (3.1%) total withdrawals</td>
<td>Meta-analysis of this 100% female trial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dextroamphetamine: -1.1; p=0.01 from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylphenidate: -0.4; p=NS from baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson</td>
<td>DB RCT crossover</td>
<td>United States</td>
<td>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.</td>
</tr>
<tr>
<td>1980</td>
<td>design</td>
<td>Setting: regular elementary</td>
<td>classrooms</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>elementary</td>
<td>classrooms</td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose Duration Dosing schedule</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson 1980</td>
<td>NR</td>
<td>MPH, D-amphetamine, placebo for 8 weeks each</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson</td>
<td>Each subject was observed daily in his classroom setting for 16 minutes via a modified form of the Direct Observation System. Reliability data was taken by an independent observer simultaneously observing and recording the subjects.</td>
<td>Age 6-12, mean age NR</td>
<td>100% male</td>
<td>Ethnicity NR</td>
<td>NR</td>
</tr>
<tr>
<td>1980 United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Age 6-12, mean age NR</td>
<td>100% male</td>
<td>Ethnicity NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
# Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson 1980</td>
<td>NR/NR/12</td>
<td>NR/NR/12</td>
<td>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.</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson 1980</td>
<td>Blood count, platelet count, and urinalysis were obtained at beginning and end of each treatment phase. Height, weight, pulse, and blood pressure were recorded at each clinic visit. Urinalysis was conducted at weekly visits to determine compliance. A symptom checklist was completed during each visit to evaluate side effects.</td>
<td>NR</td>
<td>0 withdrawals; 0 withdrawals due to adverse events</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Adderall versus methylphenidate</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barkley 2000</td>
<td>RCT with crossover</td>
<td>DSM-IV criteria for ADHD</td>
</tr>
<tr>
<td></td>
<td>Single center</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall versus methylphenidate</td>
<td>NR</td>
<td>Adderall 10 mg and 20 mg&lt;br&gt;Methylphenidate 10 mg and 20 mg&lt;br&gt;Placebo</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Barkley 2000</td>
<td>NR</td>
<td>1 week, then crossover</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>Twice daily: morning and noon</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall versus methylphenidate</td>
<td>ADHD/ODD Rating Scale, Conners CPT, Stroop Word-Color Association Test, CGI</td>
<td>n=35</td>
<td>85.7% male</td>
<td>Race nr</td>
<td>Mean IQ=103.9</td>
</tr>
</tbody>
</table>
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/ eligible/ enrolled</th>
<th>Withdrawn/ lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall versus methylphenidate</td>
<td></td>
<td></td>
<td>Mean scores for Adderall 5 mg/10 mg vs methylphenidate 5 mg/10 mg vs placebo:</td>
</tr>
<tr>
<td>Barkley 2000</td>
<td>NR</td>
<td>NR/31 (89%) analyzed</td>
<td>ADHD Total: 21.3/19.0 vs 21.01/16.8 vs 21.9</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>8 (17.4%) withdrawals/lost to fu</td>
<td>ODD Total: 10.0/8.2 vs 9.7/8.2 vs 9.4</td>
</tr>
<tr>
<td>Poor 2000</td>
<td>NR</td>
<td>46 (37%) analyzed</td>
<td>Parent ratings</td>
</tr>
<tr>
<td></td>
<td>13 (37%) analyzed from language arts</td>
<td>ADHD Total: 21.9/18.1 vs 17.9/21.5 vs 22.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (43%) analyzed from math teacher ratings; 33 (94%) analyzed from lab measures</td>
<td>English Teacher</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (17.4%) withdrawn/lost to fu</td>
<td>ADHD Total: 21.5/16.4 vs 12.2/14.0 vs 17.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ODD Total: 4.7/6.1 vs 3.3/3.9 vs 4.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>In-clinic tests</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroop Word Score: 46.5/48.7 vs 46.3/49.5 vs 47.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroop Color Score: 44.5/47.7 vs 45.2/46.2 vs 44.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stroop Interference: 52.0/54.8 vs 51.8/53.2 vs 49.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPT Omissions: 7.1/15.0 vs 15.5/23.2 vs 14.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPT Commissions: 15.2/13.8 vs 16.5/15.2 vs 15.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPT Reaction Time (ms): 391.0/408.1 vs 388.3/396.3 vs 417.2</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adderall versus methylphenidate</strong></td>
<td></td>
<td>Mean scores for Adderall 5 mg/10 mg vs methylphenidate 5 mg/10 mg vs placebo:</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Barkley 2000</td>
<td>SERS</td>
<td>Parent ratings: 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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>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; &quot;...teens rated the 10 mg dose of Adderall condition as producing significantly less severe side effects than the 5 mg dose of methylphenidate&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>English Teacher (n=13)</td>
<td></td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Math Teacher</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham</td>
<td>RCT with daily crossover</td>
<td>DSM-IV diagnosis of ADHD</td>
</tr>
<tr>
<td>1999a</td>
<td>Summer Treatment Program (STP) at the State University of New York at Buffalo</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
</table>
| Pelham 1999a | NR | MPH=methylphenidate  
1) placebo at 7:30 am, 11:30 am, and 3:30 pm  
2) 0.3 mg/kg of MPH at 7:30 am, 11:30 am, and 3:30 pm  
3) 0.3 mg/kg of MPH at 7:30 am and 11:30 am with 0.15 mg/kg at 3:30 pm  
4) 0.3 mg/kg of MPH at 7:30 am only  
5) 0.3 mg/kg of Adderall at 7:30 am and at 3:30 pm  
6) 0.3 mg/kg of Adderall at 7:30 am with 0.15 mg/kg received at 3:30 pm  
7) 0.3 mg/kg of Adderall at 7:30 am only | First 2 weeks of the program served as a period of baseline observation (unclear if run-in/washout used) | Concurrent behavioral point system |

Medication received Monday through Thursday throughout a period of 6 weeks for a 24-day clinical medication assessment; resulting in ~3 days of data in each of the active drug conditions and 6 days in the placebo condition.
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age Gender Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1999a</td>
<td>Point system Classroom measures (% of points kept, percentage of assigned seatwork completed, percentage correct of seatwork, behavioral observations during seatwork period) Daily Report Cards (% of behavioral targets met) Counselor and Teacher Ratings (Inattention/Overactivity and Oppositional/Defiant subscales of the IOWA Conners Rating Scale; Pittsburgh Side Effect Rating Scale Parent Ratings: IOWA Conners Rating Scale</td>
<td>Mean age=10.3 90.5% male Race nr</td>
<td>87% with previous use of stimulant medication 9 (43.8%) with learning problems 14 (66.7%) with comorbid oppositional defiant disorder 5 (23.8%) with comorbid conduct disorder Mean IQ=109.9 Reading achievement standard score=99.1 Math achievement standard score=105.7 ADHD items endorsed in parent structured interview: Inattention (out of 9 items)=6.1, Hyperactivity/impulsivity (out of 9 items)=5.5 oppositional/defiant items endorsed in parent structured interview=4.3 Conduct disorder items endorsed in parent structured interview=2.8 Abbreviated Conners rating scale parent=20.5 Abbreviated Conners rating scale teacher=18.2 IOWA Conners teacher rating scale inattention-overactivity/oppositional-defiant: 9.6/7.5 Disruptive behavior disorders parent rating scale: Inattention=2.2, Hyperactivity/impulsivity=2.0, Oppositional/defiant=1.8, Conduct disorder=0.4 Disruptive behavior disorders teacher rating scale: Inattention=1.7, Hyperactivity/impulsivity=1.7, Oppositional/defiant=1.6</td>
</tr>
</tbody>
</table>
**Evidence Table 3. Head to Head trials in children with ADHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/ eligible/ enrolled</th>
<th>Withdrawn/ lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1999a</td>
<td>NR/NR/21</td>
<td>NR/NR/NR</td>
<td>Adderall qAM vs MPH bid vs MPH qAM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>( b = p &lt; 0.05 ) vs MPH bid; ( c = p &lt; 0.05 ) vs MPH qAM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Counselor measures</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Following activity/rules: 73.1c vs 70.6 vs 65.7b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Noncompliance: 1.2 vs 0.8 vs 1.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interruption: 4.0 vs 5.3 vs 6.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complaining: 3.0 vs 3.0 vs 5.8b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive peer behaviors: 5.5 vs 5.2 vs 6.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conduct problems: 1.7 vs 0.9 vs 0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Negative verbalizations: 3.6 vs 3.9 vs 6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IOWA Connors IQ: 3.0c vs 3.3c vs 4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IOWA Connors OD: 1.9c vs 2.2c vs 3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Classroom measures</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seatwork rules: 92.7 vs 91.9 vs 84.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peer tutoring rules: 93.9 vs 93.6 vs 90.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Computer rules: 92.3 vs 93.4 vs 89.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seatwork complete: 90.2 vs 86.1 vs 86.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seatwork correct: 90.9 vs 89.8 vs 87.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>On-task behavior: 97.1 vs 96.1 vs 94.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Disruptive behavior: 1.9 vs 2.5 vs 3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Teacher IOWA Connors IO: 0.8c vs 0.9 vs 2.0b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Teacher IOWA Connors OD: 0.7 vs 0.4 vs 1.4b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Daily Report Card: 82.8c vs 80.5 vs 69.0</td>
</tr>
<tr>
<td>Study</td>
<td>Method of adverse effects assessment</td>
<td>Adverse Effects Reported</td>
<td>Total withdrawals; withdrawals due to adverse events</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Pelham 1999a</td>
<td>Frequency with which raters endorsed any side effect as either moderate or severe on at least 1 day</td>
<td>% children rated by Counselor/Parent/Teacher as displaying side effects at a moderate-severe level on at least one day: MPH qAM vs MPH 0.3/0.3/0.15 vs MPH 0.3/0.3/0.3 vs Adderall qAM vs Adderall 0.3/0.15 vs Adderall 0.3/-/0.3</td>
<td>NR</td>
</tr>
<tr>
<td>Fair</td>
<td>Frequency with which raters endorsed any side effect as either moderate or severe on at least 1 day</td>
<td>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 vs 0/5/0 vs 0/5/0 vs 0/5/0 vs 62/29/- vs 52/29/-</td>
<td>Sleep trouble (only parent ratings): 25 vs 15 vs 20 vs 20 vs 24 vs 38 vs 33</td>
</tr>
</tbody>
</table>
# Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1999b</td>
<td>RCT with daily crossover, Summer Treatment Program (STP)</td>
<td>DSM-IV diagnosis of ADHD</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Final Report Drug Effectiveness Review Project
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Duration</th>
<th>Dosing schedule</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1999b</td>
<td>NR</td>
<td>Adderall 7.5 mg at 7:45 am and 12.5 mg at 12:15 pm</td>
<td></td>
<td>Methylphenidate 10 mg at 7:45 am and 17.5 mg at 12:15 pm</td>
<td>First 2 weeks of NR the program served as a period of baseline observation (unclear if run-in/washout used)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>NR</td>
<td>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</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Method of Outcome Assessment and Timing of Assessment</td>
<td>Age</td>
<td>Gender</td>
<td>Ethnicity</td>
<td>Other population characteristics (mean scores)</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>-----------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Pelham 1999b</td>
<td>Point system Classroom measures (% of points kept, percentage of assigned seatwork completed, percentage correct of seatwork, behavioral observations during seatwork period) Daily Report Cards (% of behavioral targets met) Recess Rule violations (rated ~4.5 hours after ingestion of morning dose) Counselor and Teacher Ratings (Inattention/Overactivity and Oppositional/Defiant subscales of the IOWA Conners Rating Scale; Pittsburgh Side Effect Rating Scale Parent Ratings: IOWA Conners Rating Scale</td>
<td>Mean age=9.6</td>
<td>84% male</td>
<td>88% white</td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1999b</td>
<td>NR/NR/25</td>
<td>NR/NR/NR</td>
<td>Adderall 7.5/12.5 vs Methylphenidate 10 mg/17.5 mg; results of ANOVA of methylphenidate vs adderall; p-value:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Classroom variables</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rule-following</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seatwork: 89.7/90.7 vs 84.3/87.8, 4.06, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peer tutoring: 95.1/95.0 vs 91.4/94.8, 3.71, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Computer: 91.1/94.4 vs 87.3/92.6, 2.80, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seatwork completion: 71.6/67.1 vs 69.5/69.2, 0.00, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Seatwork accuracy: 87.6/87.3 vs 87.9/87.1, 0.00, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Observational measures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>On-task behavior: 89.0/89.9 vs 89.2/89.6, 0.00, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Disruptive behavior: 6.4/6.4 vs 6.9/6.2, 0.15, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Daily report card: 83.8/82.8 vs 76.4/81.7, 6.63, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recess rule violations: 1.0/0.4 vs 1.3/0.7, 3.21, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Counselor ratings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>I/O: 2.4/2.2 vs 3.4/2.6, 1.4, p&lt;0.001; O/D: 1.0/0.8 vs 2.3/1.1, 13.85, p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Teacher ratings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5:00-6:00 parent ratings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>I/O: 0.9/0.5 vs 1.5/1.0, 5.25, p&lt;0.05; O/D: 0.8/0.6 vs 1.2/1.1, 4.09, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All evening parent ratings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Point system measures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Following rules: 75.4/79.9 vs 71.4/74.5, 10.38, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Attention: 68.2/68.2 vs 64.0/64.3, 5.47, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Noncompliance: 0.9/1.2 vs 2.2/0.8, 5.65, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interruption: 6.2/6.8 vs 10.6/6.7, 7.48, p=0.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complaining/whining: 2.9/2.0 vs 4.1/2.6, 4.12, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive peer behaviors: 8.1/7.8 vs 8.8/8.8, 1.82, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conduct problems: 0.4/0.2 vs 1.4/0.1, 5.17, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Negative verbalizations: 2.0/2.2 vs 6.1/2.2, 7.89, p=0.01</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Pelham 1999b | Frequency with which raters endorsed any side effect as either moderate or severe on at least 1 day | % children rated by Counselor/Parent as displaying side effects at a moderate-severe level on at least one day: Adderall 7.5 mg vs Adderall 12.5 mg vs methylphenidate 10 mg vs methylphenidate 17.5 mg  
Motor Tics  
Counselors: 8 vs 8 vs 8 vs 4  
Parents: 4 vs 8 vs 4 vs 0  
Trouble sleeping  
Counselors: n/a  
Parents: 48 vs 64 vs 32 vs 24  
Loss of appetite  
Counselors: 76 vs 80 vs 60 vs 68  
Parents: 40 vs 72 vs 8 vs 20 | 1 (4%) withdrawal due to exacerbation of pre-existing motor tics |
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronis 2003 (same as Pelham 1999a)</td>
<td>See Pelham 1999a</td>
<td>See Pelham 1999a</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose Duration</th>
<th>Dosing schedule</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronis 2003</td>
<td>See Pelham 1999a</td>
<td>See Pelham 1999a</td>
<td></td>
<td>See Pelham 1999a</td>
<td>See Pelham 1999a</td>
</tr>
<tr>
<td>(same as Pelham 1999a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronis 2003 (same as Pelham 1999a)</td>
<td>Parent affect: Positive and Negative Affect Schedule (PANAS) - comprised of two 10-item subscales (PA=positive affect, NA=negative affect)</td>
<td></td>
<td></td>
<td></td>
<td>See Pelham 1999a</td>
</tr>
<tr>
<td>Fair</td>
<td>Pleasantness, successfulness, and effectiveness ratings: Parents completed a series of questions using a 7-point Likert scale (0=very pleasant/successful/effective to 6=very unpleasant/unsuccessful/ineffective)</td>
<td></td>
<td></td>
<td></td>
<td>See Pelham 1999a</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronis 2003</td>
<td>See Pelham 1999a</td>
<td>See Pelham 1999a</td>
<td>1) Placebo/Placebo/Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2) MPH .3/.3/.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3) MPH .3/.3/.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4) MPH .3/Placebo/Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5) Adderall .3/Placebo/.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6) Adderall .3/Placebo/.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7) Adderall .3/Placebo/Placebo</td>
</tr>
</tbody>
</table>

All p-values reflect comparison to condition #1 (Placebo/Placebo/Placebo)

Positive affect (all p:NS): 1) 28.1; 2) 30.81; 3) 29.17; 4) 29.40; 5) 30.28; 6) 30.29; 7) 29.62

Negative affect (all p:NS): 1) 12.51; 2) 11.43; 3) 12.67; 4) 12.22; 5) 11.90; 6) 11.68; 7) 11.79

Parent task completion (all p:NS): 1) 2.34; 2) 1.94; 3) 2.18; 4) 2.29; 5) 2.25; 6) 1.95; 7) 2.37

Child task completion: 1) 2.46; 2) 1.61; \( p<0.01 \); 3) 2.47; 4) 2.17; 5) 1.78; 6) 1.77; \( p<0.01 \); 7) 2.17

Overall effectiveness: 1) 2.52; 2) 1.90; \( p<0.01 \); 3) 2.27; 4) 2.19; 5) 2.07; 6) 1.75; \( p<0.001 \); 7) 2.22

Pleasantness of interaction: 1) 2.76; 2) 1.65; \( p<0.01 \); 3) 2.41; 4) 2.26; \( p<0.01 \); 5) 1.67; \( p<0.01 \); 6) 1.44; \( p<0.001 \); 7) 1.98, \( p<0.01 \)
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronis 2003</td>
<td>See Pelham 1999a</td>
<td>See Pelham 1999a</td>
<td>See Pelham 1999a</td>
<td></td>
</tr>
<tr>
<td>(same as Pelham 1999a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pliszka 2000</td>
<td>RCT</td>
<td>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</td>
</tr>
<tr>
<td>Faraone 2001</td>
<td>Parallel</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Duration</th>
<th>Dosing schedule</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pliszka 2000</td>
<td>NR</td>
<td>Adderall</td>
<td></td>
<td></td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td>Faraone 2001</td>
<td>NR</td>
<td></td>
<td>&lt; 60 kg = 5-15 mg</td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td></td>
<td>&gt; 60 kg = 10-30 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Week1: single am dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>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</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>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</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>Methylphenidate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>&lt; 60 kg = 5-25 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>&gt; 60 kg = 10-50 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week1: single am dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week3: noon dose doubled if the afternoon ratings (teacher) remained impaired</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 weeks; Flexible dosing and timing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pliszka 2000</td>
<td>IOWA CTRS, Conners Global Index, CGI</td>
<td>Mean age=8.2</td>
<td>Gender nr</td>
<td>Race nr</td>
<td>IOWA CTRS I/O: 2.2</td>
</tr>
<tr>
<td>Faraone 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pliszka 2000</td>
<td>73</td>
<td>5 (8.6%) withdrawn/0</td>
<td>Adderall vs methylphenidate</td>
</tr>
<tr>
<td></td>
<td>screened/eligible unclear/enrolled</td>
<td>lost to fu/58 analyzed</td>
<td>IOWA CTRS I/O: AM: 0.44 vs 0.78; p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adderall n=20</td>
<td>PM: 0.54 vs 0.85, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylphenidate n=20</td>
<td>Average: 0.49 vs 0.81, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo n=18</td>
<td></td>
</tr>
<tr>
<td>Faraone 2001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>58</td>
<td></td>
<td>IOWA CTRS A/D: AM: 0.25 vs 0.47, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PM: 0.33 vs 0.51, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Average: 0.29 vs 0.49, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conners Global Index: 1.04 vs 1.28, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CGI Improvement: 1.6 vs 2.35, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Responders %: 90 vs 65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Final weight (kg): 37 vs 33.2, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pliszka 2000</td>
<td>Multi-Modality Treatment of ADHD; parents asked to rate severity (none, mild, moderate, severe) of facial tics, tongue movements, picking at skin, anxious, tired, headache, stomach ache, irritable, sad or tearful, and &quot;gets wild when medication wears off&quot;</td>
<td>All p=NS</td>
<td>Total withdrawals=5 (8.6%)</td>
<td></td>
</tr>
<tr>
<td>Faraone 2001</td>
<td></td>
<td>Facial tics: 1 (5%) vs 0</td>
<td>Withdrawals due to adverse events: 2 (10%) vs 1 (5%), p=NS</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Tongue movements: 1 (5%) vs 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Picking at skin: 1 (5%) vs 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxious: 1 (5%) vs 2 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tired: 2 (10%) vs 4 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headache: 2 (10%) vs 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stomach ache: 5 (25%) vs 1 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irritable: 5 (25%) 3 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sad, tearful: 5 (25%) vs 3 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Appetite loss: 3 (15%) vs 3 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gets wild when medication wears off: 7 (35%) vs 8 (40%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manos</td>
<td>CCT (Adderall and methylphenidate protocols run simultaneously)</td>
<td>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</td>
</tr>
<tr>
<td>1999</td>
<td>Crossover</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>Pediatric Assessment and Evaluation Service (PAES) of a large, urban teaching hospital</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Duration</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manos 1999</td>
<td>Oppositional defiant disorder=21.4%</td>
<td>Adderall (once daily) vs methylphenidate (twice daily)</td>
<td>1-week for each condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>Fixed dosage:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 conditions: (1) placebo; (2) 5 mg; (3) 10 mg; (4) 15 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Six dose orders were used such that the highest dose (15 mg) was given only when preceded by the moderate dose (10 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose orders were assigned in a random fashion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parents blind to dosage</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manos</td>
<td>ARS, Conners ASQ, SSQ-R</td>
<td>Mean age=10.1</td>
<td>78.6% male</td>
<td>92.8% white</td>
<td>Inattentive type=45.2%</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combined type=54.8%</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mood disorder=1.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anxiety disorder=4.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Learning disability=47.6%</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/ eligible/ enrolled</th>
<th>Withdrawn/ lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manos 1999</td>
<td>Referred=60/ eligible=NR/participated=1</td>
<td>MPH n=42 (matched by &quot;hand-selecting&quot; by age, diagnostic category and gender to Adderall group), Adderall n=42</td>
<td>&quot;Best dose&quot; comparisons of Adderall vs methylphenidate</td>
</tr>
<tr>
<td>Poor</td>
<td>59</td>
<td></td>
<td>Parent ratings (no significant differences, but p-values nr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASQ: 49.83 vs 50.64</td>
<td>ASQ: 51.47 vs 56.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ARS: 11.79 vs 10.10</td>
<td>SSQ-R, total: 1.67 vs 1.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Composite ratings: 3.50 vs 3.31</td>
<td>SSQ-R, part: 2.23 vs 2.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Teacher ratings (no significant differences, but p-values nr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ASQ: 51.47 vs 56.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SSQ-R, total: 1.67 vs 1.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SSQ-R, part: 2.23 vs 2.68</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manos 1999</td>
<td>SE/BMS</td>
<td>Results described as &quot;no differences&quot;, but p-values nr</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>Insomnia: 5 (11.9%) vs 2 (4.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased appetite: 0 vs 1(2.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tics/nervousness: 0 vs 0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR versus SR formulations of methylphenidate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bergman 1991</td>
<td>CCT</td>
<td>DSM-III diagnosis of Attention Deficit Disorder with Hyperactivity (ADDH)</td>
</tr>
<tr>
<td>United States</td>
<td>Crossover</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Setting NR</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
</table>
| Bergman 1991  | 11 (26.2%) met criteria for reading disability (ADHD/RD) based on Reading Quotient index which calculated by dividing the Wide Range Achievement Test-Revised (WRAT-R) Reading test score by the WISC-R Full Scale IQ score. If the resulting RQ score was less than 0.85, indicating a discrepancy of more than 1 SD between reading and IQ scores, the subject was categorized as reading disabled (ADHD/RD) | Sustained-release methylphenidate 20 mg (single morning dose)  
Short-acting (regular) methylphenidate 10 mg (twice daily - morning and afternoon) | NR/NR | NR |
| United States | Poor                                                                         | Placebo                                                                | 1 day                 |                                        |

**IR versus SR formulations of methylphenidate**
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR versus SR formulations of methylphenidate</td>
<td>Identical Pairs version of the CPT (CPT-IP)</td>
<td>Mean age nr NR (between 6 and 12)</td>
<td>NR</td>
<td>NR</td>
<td>100% male</td>
</tr>
<tr>
<td>Bergman 1991 United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity nr</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>IR versus SR formulations of methylphenidate</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergman 1991 United States Poor</td>
<td>NR/NR/42 NR/NR/NR</td>
<td>SR methylphenidate = short-acting methylphenidate on all measures (data nr)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR versus SR formulations of methylphenidate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bergman 1991 United States</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Evidence Table 3. Head to Head trials in children with ADHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzpatrick 1992</td>
<td>Study design unclear</td>
<td>Diagnosis of ADD in the Diagnostic Instrument for Childhood and Adolescence (DICA)</td>
</tr>
<tr>
<td>Poor quality</td>
<td>Setting NR</td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzpatrick</td>
<td>63.1% oppositional disorder</td>
<td>Per-protocol dosages for patients &lt; 30 kg / &gt; 30 kg / mean dosages:</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td>1992</td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sustained-release (SR) methylphenidate 20 mg am / 20 mg am / mean=20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standard (SA) methylphenidate: 7.5 mg in am and pm / 10 mg in am and pm / mean=17.1 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor quality</td>
<td>Each phase lasted 2 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzpatrick</td>
<td>Conners Hyperactivity Index; IOWA Inattention/Overactivity and Aggression/Noncompliance Scales; Hyperactivity, Attention, and Aggression Subscales of Time on Task Scale (TOT); parents and teachers answered open-ended questions about child's behavior, academics, relations with others, concentration, and attitude toward school and responses rated by blinded rater as +1=positive, 0=blank/irrelevant/neutral, -1=negative responses; Continuous Performance Test (CPT) - administered 1 and 3 hours after each dose (target=2 identical numbers); Paired-associate learning (PAL) test</td>
<td>Mean age=8.71</td>
<td>Weight=31.45 kg</td>
</tr>
<tr>
<td>1992</td>
<td></td>
<td>89.5% male</td>
<td>Wechsler Scale IQ=114.11</td>
</tr>
<tr>
<td>Poor quality</td>
<td></td>
<td>Race nr</td>
<td>Peabody Individual Achievement Scale=105.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conners Hyperactivity Index-Parent/Teacher: 1.79/1.74</td>
<td>Conners Hyperactivity Index-Parent/Teacher: 0.88/0.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IOWA Inattention-Overactivity-Parent/Teacher=2.01/2.09</td>
<td>TOTS Aggression-Parent/Teacher: 0.86/0.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IOWA Aggression/Noncompliance-Parent/Teacher: 1.27/1.18</td>
<td>TOTS Hyperactivity-Parent/Teacher=0.32/0.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TOTS Attention Parent/Teacher=0.32/0.46</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/ eligible/enrolled</th>
<th>Withdrawn/ lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzpatrick 1992</td>
<td>NR/NR/19</td>
<td>NR/NR/NR</td>
<td>SR vs SA vs Combination (SR+SA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=NS for all</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All outcomes reported for Parent/Teacher</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conners: 0.98/0.77 vs 0.96/0.73 vs 0.81/0.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inattention-Overactivity: 0.98/0.92 vs 1.01/0.87 vs 0.79/0.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Noncompliance: 0.84/0.43 vs 0.80/0.48 vs 0.62/0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aggression: 0.68/0.31 vs 0.56/0.24 vs 0.60/0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity: 0.22/-0.12 vs 0.20/-0.16 vs 0.18/-0.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Attention: 0.72/0.88 vs 0.81/1.01 vs 0.91/1.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Comments valence: -0.05/0.20 vs 0.17/0.19 vs 0.18/0.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other ratings:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parent ranks: 2.16 vs 2.18 vs 1.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Laboratory rating: 0.13 vs 0.13 vs 0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight (kg): 31.59 vs 31.41 vs 31.33</td>
</tr>
</tbody>
</table>

Poorest quality
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzpatrick 1992</td>
<td>Parents interviewed concerning 12 side effects relevant to stimulant therapy and a side effect was counted if it was prevalent to a marked extent during the latter part of the 2-week period</td>
<td>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</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1987</td>
<td>RCT</td>
<td>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</td>
</tr>
<tr>
<td>Poor</td>
<td>Crossover</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Summer Treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Program</td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1987</td>
<td>4 (30.8%) with Conduct Disorder, 6 (46.1%) with Oppositional Defiant Disorder, 3 (23.1%) with Learning Disability</td>
<td>Placebo (twice daily), Methylphenidate 20 mg (twice daily), Sustained release methylphenidate 20 mg (once daily)</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>Condition varied daily and 5 to 9 days of data were gathered per medication condition</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham</td>
<td>Daily Frequencies=frequencies with which numberous appropriate and inappropriate behaviors occurred daily</td>
<td>Mean age=8.8</td>
<td>100% male</td>
<td>Race NR</td>
<td>WISC-R IQ=95.3</td>
</tr>
<tr>
<td>1987</td>
<td>Time out=average number of time outs per day</td>
<td></td>
<td></td>
<td></td>
<td>ACRS Parent/Teacher=17.7/19.0</td>
</tr>
<tr>
<td>Poor</td>
<td>Classroom measures=rates of on-task behavior; 2-minute, timed arithmetic drill, 10-minute, timed reading task (number attempted and percentage correct)</td>
<td></td>
<td></td>
<td></td>
<td>IOWA CTRS</td>
</tr>
<tr>
<td></td>
<td>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)</td>
<td></td>
<td></td>
<td></td>
<td>Inattention/Overactivity=11.9</td>
</tr>
<tr>
<td></td>
<td>Daily Report Card=Percentage of days that the child reached daily report criterion</td>
<td></td>
<td></td>
<td></td>
<td>Aggression=8.9</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
<td></td>
<td></td>
<td>Woodcock-Johnson Achievement Test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reading=91.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mathematics=97.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Language=91.4</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
</table>
| Pelham 1987 Poor | NR/NR/13 | NR/NR/NR | Methylphenidate vs sustained release methylphenidate, t-test, p-value:  
  Daily frequencies  
  Following rules: 3.5 vs 4.3; t=1.8, p=NS  
  Noncompliance: 3.4 vs 4.3; t=-2.5, p<0.05  
  Positive peer behaviors: 100.2 vs 95.8; t=0.8, p=NS  
  Conduct problems: 0.3 vs 0.4; t=-0.4, p=NS  
  Negative verbalizations: 3.4 vs 4.8; t=-2.3, p<0.05  
  N. of time outs/day: 0.5 vs 0.7; t=-1.2, p=NS  
  Classroom  
  % on task: 95.2 vs 96.5; t=0.6, p=NS  
  % on following rules: 93.9 vs 92.2; t=0.6, p=NS  
  Timed math  
  No. attempted: 21.0 vs 21.7; t=-0.5, p=NS  
  % correct: 93.4 vs 94.4; t=-0.5, p=NS  
  Timed reading  
  No. attempted: 19.8 vs 18.2; t=1.4, p=NS  
  % correct: 79.8 vs 77.9; t=0.4, p=NS  
  Seatwork  
  % completion: 86.1 vs 89.1; t=0.9, p=NS  
  % correct: 83.7 vs 82.9; t=0.3, p=NS  
  Teacher rating: 1.9 vs 3.4; t=-1.3, p=NS  
  Counselor rating: 106.4 vs 105.9; t=0.1, p=NS  
  Positive daily report card (% of days received): 83.2 vs 81.8; t=0.2, p=NS  
  Observed interactions  
  Positive peer: 97.9 vs 95.2; t=1.6, p=NS  
  Negative peer: 1.4 vs 1.5; t=-0.2, p=NS  
  No interactions: 0.7 vs 3.3; t=-1.8, p=NS |
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1987</td>
<td>NR</td>
<td>Evidence of anorexia: Standard methylphenidate=4 (30.8%) vs 5 (38.5%); p=NS</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 2001</td>
<td>RCT, DB, crossover</td>
<td>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.</td>
</tr>
<tr>
<td>Fair</td>
<td>Setting: regular home and school settings Sunday-Friday; study site for Saturday laboratory sessions from 6:45 AM to 8:15 PM</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Comorbidity</td>
<td>Interventions and total daily dose</td>
</tr>
<tr>
<td>------</td>
<td>---------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Pelham 2001 | Oppositional defiant disorder=43% Conduct disorder=37% | Placebo  
Methylphenidate immediate release, three times daily (7:30 AM, 11:30 AM, 3:30 PM), average dose=29 mg (0.88 mg/kg)  
Methylphenidate extended release (Concerta), once daily in the morning (7:30 AM), average dose=35 mg (1.05 mg/kg)  
Flexible dosing determined based on that child's MPH dosing before the study  
Double-dummy placebo design  
7 days, then crossover | NR/NR | 4-6 sessions of behavioral parent training was provided (how to use behavioral techniques in the home setting); teacher received 1-4 clinical contacts during which a consulting teacher worked with each child's teacher to establish a daily report card (DRC) and to consult on other classroom management strategies |
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham</td>
<td>Primary outcome measures: (1) IOWA inattention/overactivity (I/O) in the natural setting and (2) SKAMP attention in the laboratory classroom</td>
<td>Mean age 9.1</td>
<td>89% male</td>
<td>94% white</td>
<td>Pre-study MPH use:</td>
</tr>
<tr>
<td>Fair</td>
<td>Other dependent measures:</td>
<td></td>
<td></td>
<td></td>
<td>BID dosing=57%; TID dosing=43%</td>
</tr>
<tr>
<td>2001</td>
<td>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</td>
<td></td>
<td></td>
<td></td>
<td>Full-scale IQ (WISC-III)=104.8</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
<td></td>
<td></td>
<td>Reading achievement (WIAT)=104.1</td>
</tr>
<tr>
<td></td>
<td>Structured recreation: 1) frequencies of rule violations, 2) frequencies of negative behaviors, 30 observed disruptive behavior, 4) observed on-task behavior, 5) records of individualized target behaviors (DRC), and 6) counselor end-of-day IOWA-Conners ratings</td>
<td></td>
<td></td>
<td></td>
<td>Math achievement (WAT)=98.8</td>
</tr>
<tr>
<td></td>
<td>Recess: 1) frequencies of rule violations, and 2) observed disruptive behavior</td>
<td></td>
<td></td>
<td></td>
<td>Spelling achievement (WAT)=96.3</td>
</tr>
<tr>
<td></td>
<td>Daily behavior: 10 % following activity rules, 2) nonc</td>
<td></td>
<td></td>
<td></td>
<td>DISC hyperactive/impulsive symptoms=8.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DISC inattention symptoms endorsed=7.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parent SNAP ratings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inattention=2.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity/impulsivity=1.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oppositional/defiant=1.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parent/DDB Ratings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inattention=2.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity/impulsivity=1.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oppositional/defiant=1.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conduct disorder=0.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parent IOWA Conners ratings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inattention/overactivity=10.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oppositional/defiant=7.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parent abbreviated Conners rating</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inattention/overactivity=18.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oppositional/defiant=18.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Teacher SNAP ratings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inattention=2.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity/impulsivity=1.62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oppositional/defiant=1.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Teacher DDB ratings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inattention=1.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity/impulsivity=1.47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oppositional/defiant=0.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Teacher IOWA Conners ratings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inattention/overactivity=9.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oppositional/defiant=4.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Teacher abbreviated Conners rating</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inattention/overactivity=14.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Teacher peer relations rating</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/ eligible/enrolled</th>
<th>Withdrawn/ lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
</table>
| Pelham 2001 | NR/NR/70                    | 2 (2.8%) withdrawn/lost to fu nr/analyzed 68 5 children missed one of 3 testing sessions | Placebo / tid IR MPH / Concerta, p-value = MPH IR vs Concerta Natural setting Teacher ratings Inattentiveness 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 Inattentiveness/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"

| Fair | Natural setting | Teacher ratings | Inattentiveness/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 Inattentiveness/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 2.34; 4:35-5:00: 8.91 vs 4.61 vs 2.86

Recess measures (means) Rule violations: 7:45-8:10: 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: 7:45-8:10: 10.37 vs 7.49 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: 74.5% vs 60.2% vs 61.3%; Noncompliance: 5.76 vs 2.73 vs 2.14 Interruption: 21.6 vs 10.5 vs 10.8; 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: 7:45-8:10: 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: 7:45-8:10: 7.95 vs 6.31 vs 6.10; Oppositional/defiant: 3.63 vs 2.58 vs 2.36 Abbreviated Conners: 12.70 vs 9.91 vs 9.26; Peer interactions: 0.77 vs 0.56 vs 0.49
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 2001</td>
<td>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</td>
<td>Placebo vs qd Concerta vs tid IR MPH</td>
<td>2 (2.8%)</td>
<td>withdrawals overall (group assignment unclear)</td>
</tr>
<tr>
<td>Fair</td>
<td>Serious adverse events: 0 vs 0 vs 0</td>
<td>Motor tics: 0 vs 4/70 (5.7%) vs 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep(% patients)</td>
<td>Excellent: 12% vs 13% vs 7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motor tics: 0 vs 4/70 (5.7%) vs 0</td>
<td>Good: 57% vs 47% vs 65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep(% patients)</td>
<td>Fair: 21% vs 24% vs 21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motor tics: 0 vs 4/70 (5.7%) vs 0</td>
<td>Poor: 10% vs 16% vs 7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep(% patients)</td>
<td>Usual appetite: 59% vs 77% vs 66%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motor tics: 0 vs 4/70 (5.7%) vs 0</td>
<td>Appetite loss: 4: vs 18% vs 24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep(% patients)</td>
<td>Headache: 16 (23.2%) vs 8 (11.8%) vs 11 (15.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motor tics: 0 vs 4/70 (5.7%) vs 0</td>
<td>Abdominal pain: 8 (11.6%) vs 9 (13.2%) vs 12 (17.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep(% patients)</td>
<td>Upper respiratory tract infection: 3 (4.3%) vs 2 (2.9%) vs 3 (4.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motor tics: 0 vs 4/70 (5.7%) vs 0</td>
<td>Accidental injury: 2 (2.9%) vs 1 (1.5%) vs 3 (4.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep(% patients)</td>
<td>Vomiting: 2 (2.9%) vs 2 (2.9%) vs 2 (2.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motor tics: 0 vs 4/70 (5.7%) vs 0</td>
<td>Twitching: 0 vs 0 vs 4 (5.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep(% patients)</td>
<td>Diarrhea: 1 (1.4%) vs 0 (0.0%) vs 2 (2.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motor tics: 0 vs 4/70 (5.7%) vs 0</td>
<td>Pharyngitis: 0 (0.0%) vs 1 (1.5%) vs 2 (2.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep(% patients)</td>
<td>Rhinitis: 0 (0.0%) vs 1 (1.5%) vs 2 (2.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motor tics: 0 vs 4/70 (5.7%) vs 0</td>
<td>Dizziness: 0 (0.0%) vs 2 (2.9%) vs 1 (1.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep(% patients)</td>
<td>Urinary incontinence: 2 (2.9%) vs 0 (0.0%) vs 1 (1.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Evidence Table 3. Head to Head trials in children with ADHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox 2004</td>
<td>RCT</td>
<td>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)</td>
</tr>
<tr>
<td>Fair</td>
<td>Crossover</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox 2004</td>
<td>NR</td>
<td>Methylphenidate in equal doses at 8 am, noon, and 4 pm (mean = 60 mg)</td>
<td>24 hour washout</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylphenidate osmotic, controlled-release oral formulation (OROS) at 8 am (mean=54 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 days of dosage maintenance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox</td>
<td>Atari Research Driving Simulator Composite Score (Impaired Driving Score) consisting of Off Road, Veering Across Midline, Standard Deviation Steering, Inappropriate Braking, % Missed Stop Signs, % Bumps, and % Crashes</td>
<td>Mean age = 17.2</td>
<td>100% male</td>
<td>Race NR</td>
<td>Inattentive type = 4 (66.7%)</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combined type = 2 (33.3%)</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proportion taking medication for ADHD at baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean baseline dose of MPH NR</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox 2004</td>
<td>NR/NR/7 1 (14.3%) withdrawn/0 lost to fu/analyzed=6</td>
<td>OROS Methylphenidate vs methylphenidate TID IDS</td>
<td>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)</td>
</tr>
</tbody>
</table>

Individual parameters (F-value/p-value for MPH TID vs MPH OROS)
- Standard deviation steering: F=0.65, p=0.42
- Off Road: 2.50/0.12
- Veering across midling: 2.11/0.15
- Inappropriate braking: 4.47/0.04
- % missed stop signals: 5.76/0.02
- % bumps: 1.35/0.25
- % crashes: 3.13/0.08
- Speeding: 1.60/0.21

Standard deviation speed: 4.19/0.04
Risky Driving Means (daily driving diaries - self reported): 2.6 vs 3.2, p=NS
# Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cox 2004</td>
<td>NR</td>
<td>NR</td>
<td>1 (14.3%)</td>
<td>0 due to adverse events</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolraich 2001</td>
<td>RCT</td>
<td>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</td>
</tr>
<tr>
<td>United States</td>
<td>Parallel Multicenter</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Duration</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolraich 2001</td>
<td>46.5% ODD 11.3% Conduct Disorder 5.3% Tic Disorder 1.4% Anxiety Disorder 0.7% Depression</td>
<td>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)</td>
<td>Duration=4 weeks</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
</table>
| Wolraich  | 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 years  
82.6% male  
84.4% White  
7.4% Black  
0.4% Asian  
3.5% Hispanic | ADHD Diagnosis  
73.4% combined  
19.5% inattentive  
7.1% hyperactive/impulsive  
Previous stimulant therapy  
20.2% None  
6.4% Not in previous 4 weeks  
5.7% Non-MPH  
67.7% MPH |
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/ eligible/enrolled</th>
<th>Withdrawn/ lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
</table>
| Wolraich 2001          | Screened=50, Enrolled=405, Randomized=312 | Withdrawn=206 (66%), Lost to follow-up=1(0.3%), Analyzed=277 (MPH n=94, MPH OROS n=94, Placebo n=89) | Mean change in IOWA Conners Scores (OROS MPH vs IR MPH) (p-values NR, but narrative states there are NS differences):  
  Teacher/Parent scores:  
  Inattention/Overactivity: -3.76/-4.79 vs -3.59/-3.73  
  Oppositional/Defiance: -1.6/-3.24 vs -1.3/-2.36  
  Mean changes in secondary measures of efficacy (teacher ratings)  
  Peer Interaction: -0.33 vs -0.21  
  SNAP-IV Inattention: -0.69 vs -0.80  
  SNAP-IV Hyperactivity/Impulsivity: -0.64 vs -0.69  
  SNAP-IV Oppositional Defiant Disorder: -0.36 vs -0.32  
  Global Efficacy at end of study: 1.42 vs 1.43  
  Mean change in secondary measures of efficacy (parent ratings)  
  SNAP-IV Inattention: -0.91 vs -0.77  
  SNAP-IV Hyperactive/Impulsive: -0.91 vs -0.74  
  SNAP-IV Oppositional Defiance Disorder: -0.65 vs -0.41  
  Global Efficacy at end of study: 1.47 vs 1.28  
  Investigator ratings  
  Mean CGI at end of study: 4.24 vs 4.19  
  % of patients on CGI rated as "much" or "very much" improved: 46.7% vs 47.2%  
  Other  
  Global assessment of efficacy, % patients teachers/parents rated as "good or excellent": 42.9%/54.0% vs 46.9%/46.5%  
  CGI, % patients rated as "very much improved or much improved": 46.7% vs 47.2%  
  Parent Satisfaction Questionnaire (% pleased/very pleased/extremely pleased): 62.6% vs 64% |
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolraich</td>
<td>AEs collected at days 7, 14 and 28 by asking parents whether any new development 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.</td>
<td>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 &quot;similar&quot;. New onset tics (# patients): 0 vs 1 (1%), p=NS.</td>
<td>Withdrawals due to adverse events: 1% vs 1%. Total withdrawals: 15 (16%) vs 13 (13.8%).</td>
<td>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.</td>
</tr>
<tr>
<td>2001 United States Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Although the numbers enrolled vs analyzed are described in the text and in a figure, they are confusing and difficult to reconcile with each other.
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitehouse</td>
<td>RCT</td>
<td>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</td>
</tr>
<tr>
<td>1980, United States</td>
<td>Parallel</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>Double-blind, Setting NR</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitehouse 1980</td>
<td>NR</td>
<td>Standard methylphenidate 20 mg (twice daily)</td>
<td>Run-in: one month of standard methylphenidate 20 mg (twice daily)</td>
<td>NR</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td>Sustained-release methylphenidate 20 mg (once daily)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Duration=2 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosing schedule: 30 minutes prior to breakfast; 30 minutes before lunch</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Evidence Table 3. Head to Head trials in children with ADHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
</table>
| Whitehouse  | Bender Visual Motor Gestalt  
1980 United States  
Fair  
Physician questionnaire (not described) completed at visits 1, 2 and 3  
Teacher questionnaire (not described) completed within 4 days prior to the patients entering the study and again 4 days before the final visit | Mean age=8.5  
83.3% male  
86.7% white  
13.3% black | Height (inches)=50  
Weight (pounds)=57.8  
Right-handedness=90%  
Physician Questionnaire Overt Signs of Tension: 1.63 (2.00 vs 1.21; p<0.05)  
Teacher questionnaire Tension/Anxiety: 10.9 (10.00 vs 12.00; p<0.05) |
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/ eligible/ enrolled</th>
<th>Withdrawn/ lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
</table>
| Whitehouse    | NR/NR/34                     | 4 (11.8%) withdrawn/0 lost to fu/30 analyzed | Mean change scores (visit 3 compared to visit 1) for sustained release vs standard:  
Teacher  
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  
Parent Questionnaire  
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 |
| 1980 United States |                               |                                |                                                                        |
| Fair          |                               |                                |                                                                        |
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitehouse</td>
<td>NR</td>
<td>Adverse reactions: 5 (31.3%) vs 2 (14.3%), p=NS (consisted of headache, hyperactivity and restlessness)</td>
<td>4 (11.8%) (group assignment NR)</td>
<td>No withdrawals due to adverse events</td>
</tr>
<tr>
<td>1980 United States</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clonidine versus Methylphenidate</strong></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Tourette's Syndrome Study Group 2002</td>
<td>RCT Parallel Multicenter</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clonidine versus Methylphenidate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tourette's Syndrome Study Group 2002</td>
<td>Tourette's syndrome Other psychiatric diagnoses OCD: 15.8% ODD: 38.1% Conduct disorder: 9% GAD: 9.2% MDD: 5%</td>
<td><strong>Mean doses:</strong> Clonidine 0.25 mg Methylphenidate 25.7 mg Combination (clonidine+methylphenidate) 0.28 mg and 26.1 mg Placebo</td>
<td>NR/NR</td>
<td>Nonpharmacologic (e.g., behavioral) interventions were allowed, but remained unchanged throughout the course of the study</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>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,</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Final Report Drug Effectiveness Review Project

Pharmacologic Treatments for ADHD Page 182 of 616
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clonidine versus Methylphenidate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tourette's Syndrome Study</td>
<td>ASQ-Teacher, Iowa CTRS, ASQ-Parent, Conners CPT; systematic classroom observations of the subject's behavior; Yale Global Tic Severity Scale (YGTSS); Tic Symptom Self Report Scale (TSSR); Global Tic Rating Scale (GTRS); Child-Yale Brown Obsessive Compulsive Scale (C-YBOCS); Children's Global Assessment Scale (C-GAS)</td>
<td>Mean age=10.2</td>
<td>85.4% male</td>
<td>88.3% white</td>
<td>Tic Disorder Diagnosis: Tourette syndrome: 94%; Chronic motor tic disorder: 5%; Chronic vocal tic disorder: 1%; ADHD subtype: Inattentive: 71.3%; Hyperactive/impulsive: 2.3%; Combined: 26.4%; Mean rating scale scores: ASQ-Teacher: 14.6, ASQ-Parent: 18.1, IOWA CTRS I/O, O/D, Total: 9.1, 3.8, 12.9, YGTSS Motor, Verbal, Total: 11.3, 9.0, 40.6, GTRS Teacher, Parent: 8.6, 11.0; Classroom observations: On-task behavior: 76.7%, Disruptive behavior: 10.9%</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine versus Methylphenidate</td>
<td>NR/148/136</td>
<td>19 (14%) withdrawn/0 lost to fu/136 analyzed</td>
<td>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&lt;0.0001 ASQ-Parent: 4.7, p=0.009; 5.5, p=0.002, 5.9, p=0.002 Iowa Connors 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&lt;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 Connors CPT Commissions: 0.8, p=NS; 2.6, p=NS; 3.2, p=NS Hit Rnx. 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&lt;0.0001</td>
</tr>
<tr>
<td>Tourette's Syndrome Study Group 2002</td>
<td>Fair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clonidine versus Methylphenidate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tourette's Syndrome Study NR Group</td>
<td>NR</td>
<td>Clonidine vs methylphenidate</td>
<td>MPH=4 (10.8%)</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td>Sedation (% patients): 48% vs 14%; p=0.004</td>
<td>Clonidine=4 (11.8%)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Sedation (% patients rated as moderate or severe): 35% vs 8%; p=0.007</td>
<td>Combination=4 (12.1%)</td>
<td>Withdrawals due to adverse events Combination=1 (3.4%) for ECG change; no other withdrawals due to adverse events in other groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total Withdrawals</td>
<td>Placebo=7 (21.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comments</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Meere 1999</td>
<td>6 (11.3%) Conduct Disorder</td>
<td>Methylphenidate 0.6 mg/kg, Clonidine 4.0 μg/kg (using 25 μg Dixarit dragees)</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td>The Netherlands Fair</td>
<td>14 (26.4%) Oppositional Defiant Disorder</td>
<td>7 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (3.8%) Depressive/Anxiety Disorder</td>
<td>Twice daily dosing: Methylphenidate=breakfast/lunch; Clonidine=breakfast/evening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connor 2000 US</td>
<td>ODD or CD</td>
<td>Clonidine maximum, flexibly titrated based on clinical efficacy and reported side effects, of 0.3 mg three times daily (mean dose 0.17 mg/d) vs Methylphenidate (MPH) maximum, flexibly titrated based on clinical efficacy and reported side effects, of 40 mg twice daily (mean dose 32.5 mg/d)</td>
<td>48 hour open drug washout before screening</td>
<td>All were free of medication at baseline.</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Meere 1999</td>
<td>NR/NR/53</td>
<td>NR/NR/53</td>
<td>Two-way MANOVA (groups, session)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean RT: F(2, 50) = 1.83, p&lt;0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Errors: F(2, 50) = 0.69, p&lt;0.51</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td>Contrast MANOVA analysis for each condition separately for RT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MPH vs Clonidine: F(1,33) = 4.6, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Variability of responding: F(2, 50) = 2.02, p&lt;0.15</td>
</tr>
<tr>
<td>Connor 2000</td>
<td>NR/NR/24</td>
<td>0/0/24</td>
<td>Clonidine only (n=8) vs Methylphenidate (MPH) only (n=8) [MPH and clonidine combined (n=8) results are not included here]</td>
</tr>
</tbody>
</table>

**Parent Ratings**
No interaction was found to be significant for group X time.

**Teachers Ratings**
SSQ Number of Problem Settings
<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>van der Meere 1999</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>The Netherlands</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connor 2000 US</td>
<td>Number and severity of side effects were reported by parents and teachers. Pulse, systolic and diastolic blood pressure, EKG data, height, and weight were analyzed.</td>
<td>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.</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extended release formulations of Methylphenidate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopez</td>
<td>RCT</td>
<td>Children who met ADHD criteria based on the Diagnostic Interview Schedule for Children</td>
</tr>
<tr>
<td>2003</td>
<td>Crossover Simulated school setting (18 children per classroom)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>Single-blind (medicating nurse unblinded; but all other study personnel and patients were blinded)</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose Duration Dosing schedule</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Extended release formulations of Methylphenidate</em></td>
<td></td>
<td>Methylphenidate osmotic controlled release delivery system (MPH OROS) 18 mg or 36 mg Methylphenidate spheroidal oral drug absorption system (MPH SODAS) 20 mg Placebo</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lopez 2003</td>
<td>NR</td>
<td>5-single dose test sessions (one practice visit, three active treatments and placebo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extended release formulations of Methylphenidate</strong></td>
<td>(1) Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale (SKAMP): Attention, Deporment, and Combined Ratings subscales</td>
<td>Mean age=9.0</td>
<td>80.5% male</td>
<td>36% White</td>
<td>NR</td>
</tr>
<tr>
<td>Lopez 2003</td>
<td></td>
<td>36% Hispanic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>(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</td>
<td>27% African</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>36% Hispanic</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Evidence Table 3. Head to Head trials in children with ADHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extended release formulations of Methylphenidate</strong></td>
<td></td>
<td></td>
<td>MPH SODAS 20mg vs MPH OROS 18mg vs MPH OROS 36mg vs Placebo; p-values reflect comparison to MPH SODAS</td>
</tr>
<tr>
<td>Lopez 2003</td>
<td>NR/NR/36</td>
<td>0 withdrawn/0 lost to fu/36 analyzed</td>
<td>Mean change from baseline for SKAMP-attention</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC(0-4): -2.48 vs -1.36 (p=0.015) vs -1.55 (p=0.043) vs 1.24 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC(0-8): -4.48 vs -2.72 (p=NS) vs -3.24 (p=NS) vs 3.79 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Greatest improvement: 54% at 2 hrs vs 35% at 1 hour vs 35% at 3 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean change from baseline for SKAMP-deportment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC(0-4): -1.67 vs -0.28 (p&lt;0.001) vs -0.55 (p=0.004) vs 0.95 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC(0-8): -2.81 vs -0.82 (p=0.018) vs -1.34 (p=0.078) vs 2.85 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Greatest improvement: 63%/2 hrs vs 32%/8 hrs vs 40%/6 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean change from baseline for SKAMP-combined</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC(0-4): -2.05 vs -0.78 (p&lt;0.001) vs -1.01 (p=0.003) vs 1.09 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC(0-8): -3.58 vs -1.70 (p=0.01) vs -2.22 (p=0.061) vs 3.28 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Math test-attempted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC(0-4): 112 vs 62 (p=0.066) vs 69 (p=NS) vs -39 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC(0-8): 202 vs 115 (p=NS) vs 137 (p=NS) vs -123 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Greatest improvement: 52%/2 hrs/41% at 1 hr; 26%/8 hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Math Test Correct</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC(0-4): 104.07 vs 45.44 (p=0.026) vs 58.55 (p=0.080) vs -40.6 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AUC(0-8): 183 vs 100 (p=NS) vs 117 (p=NS) vs -124.7 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Greatest improvement: 52%/2 hrs vs 39%/1 hr vs 26%/8 hrs</td>
</tr>
</tbody>
</table>
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez 2003</td>
<td>NR</td>
<td>Number (proportion) patients with at least one adverse event: 1 (2.7%) vs 1 (2.7%) vs 1 (2.7%)</td>
<td>Total withdrawals=0</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td>Withdrawals due to adverse events=0</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conners, 1980</td>
<td>RCT DB, parallel. Setting:</td>
<td>Children aged 6-11.75 years, IQ &gt;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.</td>
</tr>
</tbody>
</table>
**Evidence Table 3. Head to Head trials in children with ADHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conners, 1980</td>
<td>NR</td>
<td>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.</td>
<td>None/8 day washout for hyperkinesis medications and 6 months for phenothiazines</td>
<td>None</td>
</tr>
</tbody>
</table>

Patients were stabilized on their dose between weeks 4 and 8. The trial was 10 weeks long.
**Evidence Table 3. Head to Head trials in children with ADHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conners, 1980</td>
<td>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</td>
<td>Age: 7.9 years (range 6-11 years)</td>
<td>Male: 57 (95%)</td>
<td>White: 59 (98%)</td>
<td>African-American: 1 (2%)</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other comparisons to methylphenidate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conners, 1980</td>
<td>88/NR/60</td>
<td>NR/NR/60</td>
<td></td>
</tr>
</tbody>
</table>

**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 (62.38-61.32) vs -2.09 (34.00-61.06)
- **Correct responses:** -6.44 (27.62-34.06) vs -10.62 (28.75-39.37) vs -0.97 (19.56-18.59)
- **Errors of omission:** 4.36 (20.75-16.39) vs 9.36 (21.31-11.95) vs 3.82 (6.88-18.59)
- **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)
- **Impatience:** 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)
- **Obsession:** 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=17

- **Conduct problem:** 0.58 (1.11-0.53) vs 0.61 (1.29-0.68) vs 0.11 (0.82-0.71)
- **Inattentive-passive:** 0.80 (1.87-1.07) vs 0.66 (1.86-1.20) vs 0.40 (1.65-1.25)
- **Anxiety:** 0.09 (0.65-0.56) vs 0.25 (0.96-0.71) vs 0.23 (0.81-0.58)
- **Hyperactivity:** 0.86 (1.90-1.04) vs 0.96 (2.24-1.28) vs 0.45 (1.90-1.45)
- **Sociability:** 0.121 (0.53-0.41) vs 0.17 (0.88-0.71) vs -0.14 (0.76-0.90)
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conners, 1980</td>
<td>An ongoing record was obtained from twice-weekly phone calls to parents and physician completed a 49-item checklist of side effects on the Physician's Rating Sheet (done at weeks 4 and 8). Parents also rated their child on a 50-item checklist.</td>
<td>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.</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kratochvil 2002</td>
<td>Open-label Parallel</td>
<td>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)</td>
</tr>
<tr>
<td>United States/Canada</td>
<td>Multicenter Outpatient</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kratochvil 2002</td>
<td>Oppositional/defiant disorder = 52.6% Major depressive disorder = 6.6% Elimination disorder = 16.7%</td>
<td>Atomoxetine CYP 2D6 extensive metabolizers: ttitated 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</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kratochvil 2002</td>
<td>Primary measure: Investigator-rated ADHD RS; Secondary measures: Parent-rated version of the ADHD RS, Conners Parent Rating Scale-Revised: Short Form (CPRS-R), Clinical Global Impression-ADHD-Severity scale</td>
<td>Mean age=10.4</td>
<td>92.5% male</td>
<td>ADHD subtype</td>
</tr>
<tr>
<td>United States/Canada</td>
<td>ADHD RS; Conners Parent Rating Scale-Revised: Short Form (CPRS-R); Clinical Global Impression-ADHD-Severity scale</td>
<td>76.7% white</td>
<td></td>
<td>Combined: 75.9%</td>
</tr>
<tr>
<td>Fair</td>
<td>ADHD-Severity scale</td>
<td></td>
<td></td>
<td>Hyperactive-impulsive: 1.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inattentive: 22.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADHD RS-Parent scored (mean): 76.7</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kratochvil 2002</td>
<td>319/NR/228</td>
<td>85 (37.3%) with 5 (2.2%)</td>
<td>Atomoxetine vs methylphenidate (mean changes) (p=NS for all)</td>
</tr>
<tr>
<td>United States/Canada</td>
<td></td>
<td></td>
<td>ADHD RS Total score: -19.44 vs -17.78</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>lost to fu/218 analyzed (atomoxetine n=178; methylphenidate n=40)</td>
<td>ADHD RS Hyperactivity/Impulsivity: -9.50 vs -8.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADHD RS Inattention subscale: -9.94 vs -9.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CGI-ADHD-Severity score: -1.67 vs -1.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPRS-R ADHD Index: -11.36 vs -11.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPRS-R Cognitive: -6.17 vs -5.69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPRS-R Hyperactive: -5.56 vs -4.78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADHD RS-Parent Total T score: -18.83 vs -18.38</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kratochvil</td>
<td>Administration of open-ended questions and collection of ECG and laboratory data</td>
<td>Atomoxetine vs methylphenidate; p=NS unless otherwise noted</td>
<td>Total withdrawals: 66 (35.9%) vs 19 (43.2%); p=NS</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td>Headache: 57 (31%) vs 13 (32.5%)</td>
<td>Withdrawals due to adverse events: 10 (5.4%) vs 5 (11.4%); p=NS</td>
<td></td>
</tr>
<tr>
<td>United States/Canada</td>
<td></td>
<td>Abdominal pain: 43 (23.4%) vs 7 (17.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Anorexia: 35 (19%) vs 6 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhinitis: 33 (17.9%) vs 8 (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nervousness: 29 (15.8%) vs 4 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting: 22 (12%) vs 0, p=0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever: 20 (10.9%) vs 4 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Somnolence: 20 (10.9%) vs 0, p=0.029</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea: 19 (10.3%) vs 2 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia: 17 (9.2%) vs 7 (17.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asthenia: 14 (7.6%) vs 1 (2.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhea: 13 (7.1%) vs 1 (2.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emotional lability: 11 (6%) vs 2 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pharyngitis: 11 (6%) vs 3 (7.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia: 11 (6%) vs 2 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accidental Injury: 10 (5.4%) vs 5 (12.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cough increased: 10 (5.4%) vs 2 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyspepsia: 10 (5.4%) vs 2 (5.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain: 10 (5.4%) vs 1 (2.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flu syndrome: 9 (4.9%) vs 4 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection: 8 (4.3%) vs 3 (7.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rash: 7 (3.8%) vs 3 (7.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depression: 5 (2.7%) vs 2 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight loss: 5 (2.7%) vs 2 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperkinesia: 3 (1.6%) vs 2 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palpitation: 3 (1.6%) vs 2 (5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thinking abnormal: 0 vs 2 (5%); p=0.031</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buitelaar 1996</td>
<td>RCT</td>
<td>Crossover</td>
<td>(1) Diagnosis of ADHD according to DSM-III-R criteria; (2) scores in the clinical range on both the CBCL and CTRS hyperactivity factors; (3) deficits in attention performance on either a reaction-time task or a continuous performance task in the neuropsychological testing; (4) no previous treatment with psychotropic medication; and (5) a clinical indication for drug treatment</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>CCT</td>
<td>Utrecht Department of Child Psychiatry</td>
<td></td>
</tr>
<tr>
<td>Stephens 1984</td>
<td>Crossover</td>
<td>Patients recruited from (1) Psychology Clinic at Florida State University and (2) Hope Haven Children's Hospital in Jacksonville, Florida</td>
<td>DSM-III diagnosis of attention-deficit disorder with hyperactivity</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Duration</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buitelaar</strong></td>
<td></td>
<td>Pindolol: single dose of 20 mg for 3 days, then 40 mg (administered twice daily at breakfast and noon)</td>
<td>NR/NR</td>
<td>NR/NR</td>
</tr>
<tr>
<td>1996</td>
<td>Conduct disorder = 20</td>
<td>Methylphenidate: single dose of 10 mg for 3 days, then 20 mg (administered twice daily at breakfast and noon)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Depressive disorder = 8</td>
<td>Fixed dosing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(15%)</td>
<td>4 weeks; drug-free interval of 2 weeks; then crossover</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fair</strong></td>
<td>Anxiety disorder = 22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(42%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Stephens       | NR                           | Medication was prescribed by each child's physician (method nr)         | NR/NR                   | NR                                     |
| 1984           |                               | Pemoline 1.9 mg/kg (mean=8.7 mg)                                        |                         |                                        |
| United States  |                               | Methylphenidate 0.3 mg/kg (mean=55.5 mg)                                 |                         |                                        |
| Poor quality   |                               | Placebo                                                                 |                         |                                        |
|                |                               | Flexible dosing                                                         |                         |                                        |
|                |                               | Eight 2-day treatment periods over three weeks                         |                         |                                        |
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age Gender Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buitelaar 1996</td>
<td>Hyperactivity, conduct and anxiety factor sum scores from the 93-item Conners’ Parent Rating Scale x weeks 0, 2 and 4</td>
<td>Mean age=9.1</td>
<td>WISC-R IQ=93.2</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Mean age=9.1</td>
<td>93.7% male</td>
<td>CBCL</td>
</tr>
<tr>
<td></td>
<td>Race nr</td>
<td></td>
<td>Inattentiveness/hyperactivity=74.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Externalizing symptoms=61.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Internalizing symptoms=68.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conners' Parents' Rating Scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abbreviated scale=3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity=2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conduct=1.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conners' Teachers' Rating Scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abbreviated scale=2.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity=2.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conduct=1.4</td>
</tr>
<tr>
<td>Fair 1984 United States Poor quality</td>
<td>10-item Abbreviated Conners rating Scale (ACRS)</td>
<td>Mean age=8.8</td>
<td>ACRS mean score=17.9</td>
</tr>
<tr>
<td></td>
<td>39-item Conners Teachers' Rating Scale (CTRS)</td>
<td>86.1% male</td>
<td></td>
</tr>
<tr>
<td>Stephens 1984</td>
<td>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)</td>
<td>Mean age=8.8</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>Spelling task: nonsense words</td>
<td>Race NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testing sessions administered 2 hours after pemoline and 1 hour after methylphenidate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pharmacologic Treatments for ADHD
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buitelaar 1996</td>
<td>NR/NR/32 (see comments)</td>
<td>0 withdrawn/0 lost to fu/32 analyzed</td>
<td>Pindolol vs methylphenidate</td>
</tr>
<tr>
<td>The Netherlands</td>
<td></td>
<td></td>
<td>Results at weeks 2/4 (mean change)</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td>ACRS estimated from Figure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ACRS at clinic: nr/-0.3 vs nr/-0.05, p&lt;0.05</td>
</tr>
<tr>
<td>Stephens 1984</td>
<td>NR/NR/31</td>
<td>NR/NR/NR</td>
<td>Pemoline vs methylphenidate (p=NS for all comparisons)</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td>Mean number of total errors:</td>
</tr>
<tr>
<td>Poor quality</td>
<td></td>
<td></td>
<td>Paired associates learning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Learning: 37.80 vs 38.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Retention: 20.67 vs 20.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spelling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Learning: 27.33 vs 26.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Retention: 14.39 vs 16.42</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

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

Poor quality
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrickman</td>
<td>RCT</td>
<td>Crossover Single center: ADHD outpatient clinic</td>
<td>Diagnosis of ADHD (DSM-III-R) and be between 7 and 17 years old</td>
</tr>
<tr>
<td>1995</td>
<td>Crossover</td>
<td>Single center: ADHD outpatient clinic</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair quality</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrickman</td>
<td>Conduct disorder = 2 (13.3%)</td>
<td>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</td>
<td>No run-in/Washout of 14 days</td>
<td>NR</td>
</tr>
<tr>
<td>1995 United States</td>
<td>Oppositional defiant disorder = 2 (13.3%)</td>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair quality</td>
<td>Developmental learning disorders = 5 (33.3%)</td>
<td>Duration: 6 weeks, then 2-week washout, then crossover for 6 more weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosing schedule: Bupropion=active second dose was added at 4 pm and an active thirs dose was added at noon if needed; Methylphenidate=active second dose was added at noon and a third dose was added at 4 pm if needed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
</table>
| Barrickman 1995  | Iowa Conners Abbreviated Parent and Teacher Questionnaire (ICQ); physician-rated Clinical Global Impression (CGI) | Mean age of 11.8 | 80% male | 100% Caucasian | Treatment-naïve=5 (33.3%)  
WISC-R Full Scale IQ score=106  
WISC-R Verbal score=104  
WISC-R Performance score=108 |
<p>| United States    |                                                      |     |        |           |                                                 |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/eligible/enrolled</th>
<th>Withdrawn/lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrickman</td>
<td>NR/NR/18</td>
<td>3 (16.7%) withdrawn/0 lost to fu/15 analyzed</td>
<td>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 (&quot;significant&quot;, 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&lt;0.05, changes from baseline to other weeks similar for both drugs</td>
</tr>
</tbody>
</table>
# Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrickman</td>
<td>NR</td>
<td>Bupropion vs MPH</td>
<td>3 (16.7%) (group assignments nr)</td>
<td>Significant treatment order effects were reported</td>
</tr>
<tr>
<td>1995 United States</td>
<td></td>
<td>% patients with any adverse event: 9 (60%) vs 5 (33.3%); p=NS</td>
<td>Withdrawals due to adverse events: none reported</td>
<td></td>
</tr>
<tr>
<td>Fair quality</td>
<td></td>
<td>Drowsiness: 4 (26.7%) vs 1 (6.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue: 3 (20%) vs nr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea: 3 (20%) vs 1 (6.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anorexia: 2 (13.3%) vs nr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness: 2 (13.3%) vs nr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spaciness: 2 (13.3%) vs nr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety: 1 (6.7%) vs 1 (6.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headache: 1 (6.7%) vs 1 (6.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tremor: 1 (6.7%) vs nr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anger/crying: nr vs 1 (6.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia: nr vs 1 (6.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irritability: nr vs 1 (6.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low mood: nr vs 1 (6.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stomachache: nr vs 1 (6.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Comparisons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>James 2001 United States</td>
<td>RCT Crossover Double-blind Setting: Research</td>
<td>DSM-IV criteria for combined-type ADHD; ADHD symptoms present in at least two settings</td>
</tr>
<tr>
<td>Poor school 5 days per week</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>James 2001 United States</td>
<td>Oppositional defiant disorder=10 (28.6%) Anxiety disorder=12 (34.3%)</td>
<td>Adderall Dextroamphetamine, immediate release Dextroamphetamine spansules Placebo</td>
<td>Run-in NR/3-week washout</td>
<td>NR</td>
</tr>
<tr>
<td>Poor</td>
<td>Enuresis=3 (8.6%) Dysthymic disorder=2 (5.7%) Learning disorder=6 (17.1%)</td>
<td>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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>James 2001</td>
<td>Hyperactive/Impulsive factor of the Conners Teacher Rating Scale: teacher</td>
<td>Mean age=9.1</td>
<td>60%</td>
<td>White 18 (51.4%)</td>
<td>15 (42.8%) naïve to stimulant treatment WISC-III Verbal standard score=102.5 Performance standard score=96.6</td>
</tr>
<tr>
<td>United States</td>
<td>Hyperactivity factor of the Children's Psychiatric Rating Scale: recreation therapist scored weekly</td>
<td>18 (51.4%) White</td>
<td>9 (25.7%) African Americans 7 (20%) Latinos 1 (2.8%) Asian Americans</td>
<td>CBCL Attention Problems T score=72.5 TRF Attention Problems T score=72.3</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>Academic measures: 5-minute timed math task Conners Parent Behavior Rating Scale for the hours 4 pm to 7 pm Actometer to assess motor activity</td>
<td>7 (20%) Latinos 1 (2.8%) Asian Americans</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/ eligible/enrolled</th>
<th>Withdrawn/ lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>James 2001</td>
<td>NR/38 enrolled/35 randomized</td>
<td>0/0/35</td>
<td>Adderall vs dextroamphetamine spansules vs immediate release dextroamphetamine vs placebo; differences are insignificant unless otherwise noted</td>
</tr>
<tr>
<td>United States Poor</td>
<td></td>
<td></td>
<td>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 &gt; DEX span, p&lt;0.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPRS Hyperactivity factor score obtained between 1 PM and 3 PM: 2.8 vs 2.3 vs 2.5 vs 3.8; DEX span &gt; ADL, p=0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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 &gt; placebo (p=0.007), ADL &gt; placebo (p=0.03), DEX IR = placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total attempted math problems: 171.6 vs 187.0 vs 177.4; DEX IR &gt; placebo (p=0.01), DEX span &gt; placebo (p=0.003), ADL = placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total correct math problems: 164.6 vs 177.6 vs 167.6 vs 140.2; DEX IR &gt; placebo (p=0.01), DEX span &gt; placebo (p=0.003), ADL=placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sleep (hr): 7.6 vs 7.2 vs 7.4 vs 7.8; DEX span and DEX IR decreased sleep &gt; placebo (p&lt;0.001 and p=0.02), ADL=placebo</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
</table>
| James 2001     | Stimulant Side Effect Rating Scale: rated by nurse coordinator | SERS N#: 3.3 vs 2.9 vs 2.6 vs 2.0  
SERS-N sev: 2.7 vs 3.1 vs 2.7 vs 1.8  
SERS-P#: 6.3 vs 6.7 vs 6.4 vs 5.9  
SERS-P sev: 3.2 3.7 vs 3.2 vs 2.8  
Weight (kg): 32.6 vs 32.5 vs 32.7 vs 33.3 | 0 withdrawals; 0 withdrawals due to adverse events | 0 withdrawals; 0 withdrawals due to adverse events |
| United States  | Barkley Side Effect Rating Scale: rated by parents | Mean magnitude of adverse effects rated by parents (n=20); staff nurse (n=29) for adderall, immediate-release dextroamphetamine, dextroamphetamine spansules and placebo, uncorrected p-values from ANOVA  
Trouble sleeping: 3.5 vs 3.0 vs 3.3 vs 2.5, p=0.55; nurses didn't rate  
Nightmares: 0.6 vs 0.6 vs 0.3 vs 0.3, p=0.24  
Stomaches: 1.0 vs 0.9 vs 1.1 vs 1.0, p=0.97; 0.5 vs 0.5 vs 0.8 vs 0.4, p=0.59  
Headaches: 0.9 vs 0.8 vs 0.7 vs 1.0, p=0.89; 0.1 vs 0.2 vs 0.2 vs 0.1; p=0.41  
Tics: 0.8 vs 1.2 vs 1.4 vs 0.9; p=0.16; 0.4 vs 0.3 vs 0.3 vs 0.2, p=0.34 | 0 withdrawals; 0 withdrawals due to adverse events | 0 withdrawals; 0 withdrawals due to adverse events |
Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham</td>
<td>RCT</td>
<td>Diagnosis of ADHD based on structured parental interview and parent and teacher rating scales (not specified)</td>
</tr>
<tr>
<td>1990</td>
<td>Crossover</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1988 Western</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>Psychiatric Institute and Clinic Attention Deficit Disorder Program's Summer Treatment Program</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1990</td>
<td>Oppositional/defiant disorder = 9 (40.9%) Conduct Disorder = 4 (18.2%) Discrepancy between their Wechsler Intelligence Scale for Children-Revised IQ and their Woodcock-Johnson Achievement scores of at least one full standard deviation in either reading, arithmetic, or written language, suggesting the presence of a learning disability = 13 (59.1%)</td>
<td>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 (dexitroamphetamine spansule) 10 mg (dosed once daily) All conditions accompanied by &quot;behavior modification intervention&quot; as the &quot;primary treatment modality&quot;</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 weeks total, data collected for 3 to 6 days for each condition</td>
<td></td>
<td>Dosage time NR</td>
</tr>
</tbody>
</table>
# Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham</td>
<td>Daily Frequencies=frequencies with which numerous appropriate and inappropriate behaviors occurred daily</td>
<td>Mean age=10.39</td>
<td>100% male</td>
<td>Race NR</td>
<td>WISC-R IQ=105.68</td>
</tr>
<tr>
<td>1990</td>
<td>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 equaling positive evaluations) Daily Report Card=Percentage of days that the child reached daily report criterion Continuous Performance Task=&quot;H&quot; followed by letter &quot;T&quot;</td>
<td>ACRS - Parent/Teacher: 15.50/19.32</td>
<td></td>
<td></td>
<td>IOWS CTRS</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>Race NR</td>
<td></td>
<td></td>
<td>Inattention/Overactivity=9.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aggression=5.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Race NR</td>
<td></td>
<td></td>
<td>DSM-II-R Structured Interview for Parents</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Attention deficit disorder items=11.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Race NR</td>
<td></td>
<td></td>
<td>Oppositional/defiant disorder items=5.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conduct disorder items=1.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Race NR</td>
<td></td>
<td></td>
<td>Woodcock-Johnson Achievement Test</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reading=96.45</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Race NR</td>
<td></td>
<td></td>
<td>Mathematics=99.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Language=99.00</td>
</tr>
</tbody>
</table>
### Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Screened/ eligible/ enrolled</th>
<th>Withdrawn/ lost to fu/analyzed</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1990</td>
<td>NR/NR/22</td>
<td>NR/NR/NR</td>
<td>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</td>
</tr>
</tbody>
</table>
## Evidence Table 3. Head to Head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1990</td>
<td>NR</td>
<td>Placebo vs Methylphenidate vs sustained release methylphenidate vs pemoline vs sustained release dextroamphetamine, measures of significance NR: Teacher ratings 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 Parent ratings 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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 4. Quality assessment of head to head trials in children with ADHD

**Internal Validity**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron 1997</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Elia 1991</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Elia 1993</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Casellanos 1997</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Efron 1998</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Loss to followup: differential/high</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron 1997</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR</td>
<td>WISC-R full scale IQ &lt; 80; evidence of medical or neurological diseases, or any other Axis I psychiatric disorder, with the exception of conduct disorder, oppositional disorder, mild overanxious disorder, and specific developmental disorders</td>
</tr>
<tr>
<td>Elia 1991</td>
<td>NR</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR</td>
<td>Evidence of medical or neurological disease, or any other Axis I psychiatric disorder, with the exception of conduct disorder or oppositional disorder, and/or specific developmental disorders</td>
</tr>
<tr>
<td>Elia 1993</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR</td>
<td>WISC-R Full Scale IQ score less than 75; evidence of medical or neurological diseases; any other Axis I psychiatric disorder, except obsessive-compulsive disorder, conduct or oppositional disorder, overanxious disorder, and specific developmental disorders</td>
</tr>
<tr>
<td>Casellanos 1997</td>
<td>NR</td>
<td>No</td>
<td>Unclear</td>
<td>Poor</td>
<td>NR</td>
<td>≥ 4 weeks washout</td>
</tr>
<tr>
<td>Efron 1998</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR</td>
<td>24-hour washout</td>
</tr>
</tbody>
</table>
Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efron 1997</td>
<td>NO</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Elia 1991</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Elia 1993</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Casellanos 1997</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>Efron 1998</td>
<td>NO</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

**Internal Validity**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia 1990</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Arnold 1978</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Huestis 1975</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Gross 1976</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Borcherding 1990</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
</tbody>
</table>

Pharmacologic Treatments for ADHD
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Loss to followup: differential/high</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/eligible enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia 1990</td>
<td>NR</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Fair</td>
<td>NR</td>
<td>Evidence of medical or neurologic diseases, or any other Axis I psychiatric disorder (with the exception of conduct disorder or oppositional disorder), specific developmental disorder, or mental retardation</td>
<td>≥ 3 weeks washout</td>
</tr>
<tr>
<td>Arnold 1978</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR</td>
<td>No/Yes                                                                ешшениеаного или неврологического заболевания, или любой другой Axis I психиатрической расстройство (с оговоркой на синдром противоположного поведения или оппозитивного расстройства), или специфического развитительного расстройства, или умственной отсталости</td>
<td>2-week placebo washout</td>
</tr>
<tr>
<td>Huestis 1975</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross 1976</td>
<td>NR</td>
<td>No</td>
<td>Unclear</td>
<td>Poor</td>
<td>NR/NR/50</td>
<td>No/Yes                                                                ешшениеаного или неврологического заболевания, включая хронические моторные тики или синдром Туры, или другой primary Axis I psychiatric disorder were exclusionary</td>
<td>No/No</td>
</tr>
<tr>
<td>Borcherding 1990</td>
<td>NR</td>
<td>No</td>
<td>Unclear</td>
<td>Poor</td>
<td>NR/NR/46</td>
<td></td>
<td>No/Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elia 1990</td>
<td>NO</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Arnold 1978  
Huestis 1975  

- 65.5% were psychopharmacologically "virgin"  
- Grant from Ohio Department of Mental Health and Mental Retardation; matched dosage forms were furnished by Ciba-Geigy Pharmaceutical Corp.  
- No; high proportion of class naïve patients

<table>
<thead>
<tr>
<th>Gross 1976</th>
<th>NR</th>
<th>Yes</th>
<th>NR</th>
<th>Unclear</th>
</tr>
</thead>
</table>

Borcherding 1990  

- 28.30% Yes  
- NR  
- Yes
## Evidence Table 4. Quality assessment of head to head trials in children with ADHD

### Internal Validity

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharp 1999</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Kauffman 1981</td>
<td>NR</td>
<td>Yes</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Barkley 2000</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Reported that 20 - 31% completed each randomized order of drug administration</td>
</tr>
<tr>
<td>Pelham 1999a</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
</tbody>
</table>
**Evidence Table 4. Quality assessment of head to head trials in children with ADHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Loss to followup: differential/high</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/ Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharp 1999</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/32</td>
<td>WISC-R Full Scale IQ &lt; 80 and chronic medical or neurological diseases, including Tourette's disorder and chronic tic disorders</td>
<td>No/Yes</td>
</tr>
<tr>
<td>Kauffman 1981</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/12</td>
<td>No evidence of any neurological disorder, convulsive disorder, mental retardation, metabolic disorder, degenerative neurological disease, or deficit of hearing or sight.</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Barkley 2000</td>
<td>NR</td>
<td>No</td>
<td>1 excluded due to low IQ</td>
<td>Poor</td>
<td>NR/NR/46</td>
<td>History of (1) motor/vocal tics or Tourette's Syndrome; (2) cardiac surgery, high blood-pressure (sustained blood-pressure levels above the 95th percentile for age and sex) at baseline, or cerebral vascular accident, given the known cardiac presser effects of stimulant medication; (3) adverse reactions to stimulant medications; (4) hyperthyroidism; (5) pregnancy/lactation</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Pelham 1999a</td>
<td>NR</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Fair</td>
<td>NR/NR/21</td>
<td>No medical history that prohibited them from taking psychostimulant medication or participating in the STP academic or recreational activities</td>
<td>NR/NR</td>
</tr>
</tbody>
</table>
## Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharp 1999</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Kauffman 1981</td>
<td>NR</td>
<td>Yes</td>
<td>Ciba-Geigy Corp.</td>
<td>Yes</td>
</tr>
<tr>
<td>Barkley 2000</td>
<td>NR</td>
<td>Yes</td>
<td>Shire</td>
<td>Yes</td>
</tr>
<tr>
<td>Pelham 1999a</td>
<td>24% Yes</td>
<td></td>
<td>Shire</td>
<td>No; Summer Treatment Program with behavioral training for both children and parents</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

**Internal Validity**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1999b</td>
<td>NR</td>
<td>NR</td>
<td>Crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Pliszka 2000 Faraone 2001</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Manos 1999</td>
<td>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)</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
</tbody>
</table>

Final Report Drug Effectiveness Review Project

Pharmacologic Treatments for ADHD Page 235 of 616
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Loss to followup: differential/high</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/ Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelham 1999b</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/25</td>
<td>DISC criteria for major depression episode, manic episode, or tic disorder; history of psychosis or have signs of psychosis or significantly depressed mood on the mental status examination; BIT composite IQ &lt; 75</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Pliszka 2000 No Faraone 2001</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>73 screened/eligible unclear/enrolled 58</td>
<td></td>
<td>NR/NR</td>
</tr>
<tr>
<td>Manos 1999</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>Poor</td>
<td>Referred=60/eligible =NR/participated=15 9</td>
<td></td>
<td>NR/NR</td>
</tr>
<tr>
<td>Study</td>
<td>Class naïve patients only</td>
<td>Control group standard of care</td>
<td>Funding</td>
<td>Relevance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------</td>
<td>-------------------------------</td>
<td>---------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelham 1999b</td>
<td>NR</td>
<td>Yes</td>
<td>Shire</td>
<td>No; Summer Treatment Program with behavioral training for both children and parents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pliszka 2000</td>
<td>46 (79.3%)</td>
<td>Yes</td>
<td>Shire</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faraone 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manos 1999</td>
<td>NR</td>
<td>Yes</td>
<td>NIDA, Maternal and Child Health Program</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Evidence Table 4. Quality assessment of head to head trials in children with ADHD

## Internal Validity

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergman 1991</td>
<td>Inadequate (counterbalanced order)</td>
<td>NR</td>
<td>n/a - crossover</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Fitzpatrick 1992</td>
<td>Unclear. No use of &quot;randomized&quot; terminology; No description whatsoever of group assignment</td>
<td>NR</td>
<td>n/a - crossover</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Pelham 1987</td>
<td>NR</td>
<td>NR</td>
<td>n/a - crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Pelham 1990</td>
<td>NR</td>
<td>NR</td>
<td>n/a - crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Cox 2004</td>
<td>Yes, random numbers table</td>
<td>NR; Use of a random number table without a 3rd party may indicate lack of allocation concealment</td>
<td>n/a - crossover</td>
<td>Yes</td>
<td>Unclear (abstract states study was single-blind, no other details)</td>
<td>Unclear (abstract states study was single-blind, no other details)</td>
<td>Unclear (abstract states study was single-blind, no other details)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Loss to followup:</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergman 1991</td>
<td>NR</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Poor</td>
<td>NR/NR/42</td>
<td>NR</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Fitzpatrick 1992</td>
<td>NR</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Poor</td>
<td>NR/NR/19</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pelham 1987</td>
<td>NR</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Poor</td>
<td>NR/NR/13</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Pelham 1990</td>
<td>NR</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Poor</td>
<td>NR/NR/22</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cox 2004</td>
<td>No/No</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/7</td>
<td>History of tics or other adverse reactions to MPH, or a history of substance abuse disclosed by subject or parent</td>
<td>24-hour washout</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergman 1991</td>
<td>NR</td>
<td>Yes</td>
<td>NIMH Grants (MH 38838-05 and MH 30906-09)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Fitzpatrick 1992</td>
<td>94.7% naïve to psychotropic medication</td>
<td>Yes</td>
<td>NIMH Grant MH38118, CIBA-GEIGY provided placebo tablets</td>
<td>No</td>
</tr>
<tr>
<td>Pelham 1987</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>No, Summer Treatment Program</td>
</tr>
<tr>
<td>Pelham 1990</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>No, Summer Treatment Program+behavior modification intervention</td>
</tr>
<tr>
<td>Cox 2004</td>
<td>No</td>
<td>Yes</td>
<td>McNeil Consumer and Specialty Pharmaceuticals</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

**Internal Validity**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolraich 2001</td>
<td>Yes</td>
<td>Yes</td>
<td>Small differences (NS) : proportions with comorbidities, prior MPH IR use, inattentive vs combined ADHD</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tourette’s Syndrome Study Group 2002</td>
<td>Yes, computer-generated randomization</td>
<td>Yes, central coordinating center</td>
<td>No, differences in age, proportions of ADHD subtype, ASQ-Teacher scores, and gender</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>van der Meere 1999</td>
<td>NR</td>
<td>NR</td>
<td>Boys and girls were not equally distributed among the groups</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

#### External Validity

<table>
<thead>
<tr>
<th>Study</th>
<th>Loss to followup:</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolraich 2001</td>
<td>No/No</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>Screened=500/Enrolled=405/Randomized=312</td>
<td>Acute or serious chronic disease, were hypersensitive to methylphenidate, were having significant adverse experiences from methylphenidate, or were taking a medication that would interfere with the safe administration of methylphenidate; patients with glaucoma, Tourette's syndrome, an ongoing seizure disorder, or a psychotic disorder, as were girls who had reached menarche</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Tourette's Syndrome Study Group 2002</td>
<td>No/No</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/148/136</td>
<td>NR</td>
<td>No/No</td>
</tr>
<tr>
<td>van der Meere 1999</td>
<td>NR/NR</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/53</td>
<td>NR</td>
<td>NR/NR</td>
</tr>
</tbody>
</table>
## Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolraich 2001</td>
<td>No</td>
<td>Yes</td>
<td>Alza</td>
<td>Yes</td>
</tr>
<tr>
<td>Tourette's Syndrome Study Group 2002</td>
<td>No</td>
<td>Yes</td>
<td>NIH grant #1R01NS33654</td>
<td>Yes</td>
</tr>
<tr>
<td>van der Meere 1999</td>
<td>NR</td>
<td>Yes</td>
<td>Sophia Foundation for Medical Research and Boehringer Ingelheim BV, The Netherlands</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

**Internal Validity**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez 2003</td>
<td>NR</td>
<td>NR</td>
<td>n/a - crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Kratochvil 2002</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Buitelaar 1996</td>
<td>NR</td>
<td>NR</td>
<td>n/a - crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Loss to followup: differential/high</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez 2003</td>
<td>None</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/36</td>
<td>Children with concurrent significant medical or psychiatric illness, or substance use disorder were not permitted in the study</td>
<td></td>
</tr>
<tr>
<td>Kratochvil 2002</td>
<td>No/No</td>
<td>No; 10 (4.4%) excluded from analysis due to not having a postbaseline visit</td>
<td>No</td>
<td>Fair</td>
<td>319/NR/228</td>
<td>History of bipolar or psychotic disorders, motor tics or a family history of Tourette syndrome, substance abuse, non-response to a previous trial of MPH (significant residual symptoms after at least 2 weeks of treatment with at least 1.2 mg/kg per day) and serious medical illness.</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Buitelaar 1996</td>
<td>NR/NR</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/32</td>
<td>Diagnosis of tic disorder or pervasive developmental disorder, a family history of tic disorder, and the usual contra-indications for treatment with beta-blockers such as cardiac diseases, in particular conduction abnormalities and bradycardia, hypotension, obstructive pulmonary diseases and insulin-dependent diabetes</td>
<td>NR/NR</td>
</tr>
</tbody>
</table>
**Evidence Table 4. Quality assessment of head to head trials in children with ADHD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez 2003</td>
<td>All patients had been stabilized on an equivalent dose of 10 mg twice daily of MPH prior to study entry</td>
<td>Yes</td>
<td>Novartis Pharmaceuticals</td>
<td>Yes</td>
</tr>
<tr>
<td>Kratochvil 2002</td>
<td>No</td>
<td>Yes</td>
<td>Eli Lilly</td>
<td>Yes</td>
</tr>
<tr>
<td>Buitelaar 1996</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>No - class naïve patients only</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

#### Internal Validity

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stephens 1984</td>
<td>Not randomized; medication was prescribed by each child's physician (method nr)</td>
<td>n/a</td>
<td>n/a - crossover</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Barrickman 1995</td>
<td>NR</td>
<td>NR</td>
<td>n/a - crossover</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>James 2001</td>
<td>NR - order of dose random, but order of drug not clear</td>
<td>NR</td>
<td>n/a - crossover</td>
<td>Yes</td>
<td>Unclear - dose of DEX SR increased part way through study</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
</tbody>
</table>
# Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Loss to followup: differential/high</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/ Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stephens 1984</td>
<td>NR/NR</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Poor</td>
<td>NR/NR/36</td>
<td>No; 3 (16.7%) excluded from analysis that were dropped due to failure to cooperate</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Barrickman 1995</td>
<td>NR/NR</td>
<td>No; 3 (16.7%) excluded from analysis</td>
<td>No run-in; 14-day washout</td>
<td>Fair</td>
<td>NR/NR/18</td>
<td>IQ &lt; 70 (mental retardation) and any other major Axis I, II, or III diagnoses; seizure disorder; eating disorder</td>
<td></td>
</tr>
<tr>
<td>James 2001</td>
<td>NR/NR</td>
<td>Yes for some efficacy measures; No for CPS and side effects</td>
<td>No run-in; 3-week washout</td>
<td>Poor</td>
<td>NR/38/35</td>
<td>WISC-III Full Scale IQ less than 80; presence of a chronic medical or neurological disease including Tourette's disorder, chronic tic disorder, pervasive developments disorders, and mood anxiety disorders requiring current treatment</td>
<td></td>
</tr>
</tbody>
</table>
# Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stephens</td>
<td>Unclear for 25 (69.4%); reported that 11 were taking stimulants at time of study</td>
<td>Yes</td>
<td>NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>1984</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrickman</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>James</td>
<td>42.8% class naïve</td>
<td>Yes</td>
<td>NR</td>
<td>No, research school setting</td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------</td>
<td>----------------------------------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Whitehouse 1980</td>
<td>NR</td>
<td>NR</td>
<td>No, SR/IR on Overt signs of tension and IR&gt;SR on tension/anxiety</td>
<td>Yes</td>
</tr>
<tr>
<td>Pelham 2001</td>
<td>NR</td>
<td>NR</td>
<td>n/a - crossover</td>
<td>Yes</td>
</tr>
<tr>
<td>Simpson 1980</td>
<td>NR</td>
<td>NR</td>
<td>n/a - crossover</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Evidence Table 4. Quality assessment of head to head trials in children with ADHD

### External Validity

<table>
<thead>
<tr>
<th>Study</th>
<th>Loss to followup: differential/high</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/ Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitehouse 1980</td>
<td>None/None</td>
<td>No, 4 (11.8%) excluded from analysis; not stated which groups these 4 were assigned to</td>
<td>Yes, 4 excluded from analysis for: 2 dosage deviations, 1 viral illness, 1 &quot;other reasons&quot;</td>
<td>Fair</td>
<td>NR/NR/34</td>
<td>The presence of glaucoma, epilepsy, severe organic brain damage, mental retardation, cultural deprivation, or psychosis; hypersensitivity to methylphenidate, blindness, deafness, and marked anxiety and tension as the sole manifestations of behavior disorders were excluding factors as well</td>
<td>Run-in: one month of standard methylphenidate 20 mg (twice daily) prior to study/no washout</td>
</tr>
<tr>
<td>Pelham 2001</td>
<td>NR/NR</td>
<td>No; 2 patients excluded (2.8%)</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/70</td>
<td>Presence of any medical condition that would contraindicate the use of stimulant medication; presence of any physical condition or severe learning difficulty that would interfere with participation in the laboratory classroom assessment (WISC IQ &lt; 80); receiving additional medication (beyond MPH) for ADHD; receiving any medication having CNS effects, anticonvulsants, or investigational medications; having reached menarche; and having blood pressure at or above the 95th percentile for age and height</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Simpson 1980</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/12</td>
<td>Excluded severe emotional disorder, organic brain disease, and major medical problems (e.g., sensory impairment, chronic illness, etc.)</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Study</td>
<td>Class naïve patients only</td>
<td>Control group standard of care</td>
<td>Funding</td>
<td>Relevance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------</td>
<td>--------------------------------</td>
<td>---------</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whitehouse 1980</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelham 2001</td>
<td>No</td>
<td>Yes</td>
<td>Alza</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simpson 1980</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

**Internal Validity**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Connor 2000</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Conners 1980</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

#### External Validity

<table>
<thead>
<tr>
<th>Study</th>
<th>Loss to followup: differential/high</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/ Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connor 2000</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/24</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Conners 1980</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>88/60/60</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 4. Quality assessment of head to head trials in children with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connor 2000</td>
<td>No</td>
<td>Yes</td>
<td>UMMS Small Grants Project</td>
<td></td>
</tr>
<tr>
<td>Conners 1980</td>
<td>Unclear</td>
<td>Yes</td>
<td>NIMH and Abbott</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelsey</td>
<td>2004 Fair</td>
<td>RCT, DB</td>
<td>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.</td>
<td>Oppositional/defiant disorder: 37.6% of atomoxetine group; 29.7% of placebo group</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td>Conduct disorder: 5.3% of atomoxetine group; 1% of placebo group</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine</td>
<td>Kelsey 2004</td>
<td>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.</td>
<td>5 day washout period.</td>
<td>NR/NR</td>
<td>ADHD RS, Daily parent Ratings of Evening and Morning Behavior Revised (DPREM-B-R), Conners Global Index; Parent-Evening (GIPE), CGI ADHD-S.</td>
<td>Children aged 6-12 years/71% enrolled were male/ ethnicity NR.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>ADHD Subtypes</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine Kelsey</td>
<td>2004 Fair</td>
<td>Combined: 37.6% of atomoxetine, 67.2% of placebo</td>
<td>Atomoxetine: 260 screened/197 eligible/197 enrolled</td>
<td>Atomoxetine: 26 withdrawn, 4 lost to fu, 107 analyzed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactive/impulsive: 3.8% atomoxetine, 3.1% of placebo, Inattentive: 26.3% of atomoxetine, 29.7% of placebo</td>
<td>Placebo: 17 withdrawn, 3 lost to fu, 47 analyzed</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atomoxetine</strong></td>
<td></td>
<td><strong>Source:</strong> Atomoxetine: baseline vs endpoint vs change; Placebo: baseline, endpoint, change; 95%CI for Difference From Placebo ADHD RS (atomoxetine: n=126; placebo: n=60)</td>
</tr>
<tr>
<td>Kelsey</td>
<td>Fair 2004</td>
<td>Total score: 42.1 (9.2) vs 25.3 (14.3) vs -16.7 (14.5)<em>; 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)</em>; 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)<em>; 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)</em>; 1.6(0.8) 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)<em>; 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)</em>; 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(0.7); 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)<em>; 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 up 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)</em>; 1.3(0.7) vs 1.0(0.6) vs0.3(0.6); -0.4, -0.0 Arguing or struggling: 1.3(0.8) vs 0.7(0.7) vs -0.6(0.7)<em>; 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)</em>; 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</td>
</tr>
</tbody>
</table>
**Evidence Table 5. Placebo-controlled trials in children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Kelsey  | 2004 | measuring vital signs, ECK's, open-ended questioning about negative physical symptoms and laboratory tests. | Event: **Atomoxetine (n=131) vs Placebo (n=63)**  
- Decreased appetite: 23 (17.6)* vs 4(6.3)  
- Abdominal Pain: 20(15.3) vs 4(6.3)  
- Nausea: 15(11.5) vs 5(7.9)  
- Somnolence: 19(14.5)* vs 1(1.6)  
- Headache: 9(6.9) vs9(14.3)  
- Fatigue: 13(9.)* vs 1 (1.6)  
- Dyspepsia: 8(6.1) vs 1(1.6)  
- Vomiting: 8(6.1) vs 1(1.6)  
- Diarrhea: 2(1.5) vs 4 (6.3)  
* = p<.05 | Atomoxetine: 6  
Placebo: 1 |
<p>| Fair    |      |                                     |                          |                                                     |          |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>2002</td>
<td>RCT DB</td>
<td>Patients were at least 7 years of age but less than 13 years of age at the initial visit and were determined to be of normal intelligence based on the Weschler Intelligence Scale for Children-Third Edition (WISC-III). Patients were required to meet DSM-IV diagnostic criteria for ADHD, as assessed by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia, and have a score on the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and Scored (ADHD RS) at least 1.5 standard deviations above the age and gender norms for their diagnostic subtype (primarily inattentive or primarily hyperactive/impulsive) or the total score for the combined subtype.</td>
<td>Atomoxetine:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oppositional defiant disorder-53(41.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elimination disorders-10(7.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phobias-16(12.4%); Dysthymia-7(5.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Generalized anxiety disorder-4(3.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major depressive disorder-4(3.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oppositional defiant disorder-45(36.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Elimination disorders-15(12.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phobias-13(10.5%); Dysthymia-5(4.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Generalized anxiety disorder-3(2.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major depressive disorder-4(3.2)</td>
</tr>
<tr>
<td>Author</td>
<td>Interventions and total daily dose</td>
<td>Run-in/Washout Period</td>
<td>Method of Outcome Assessment and Timing of Assessment</td>
<td>Age</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------</td>
<td>-----------------------</td>
<td>------------------------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Spencer 2002</td>
<td>Atomoxetine 2mg/kg/day or a total 90mg/day based on therapeutic response and tolerability for 9 weeks</td>
<td>2 weeks</td>
<td>ADHD Rating Scale (ADHD RS) rated by trained clinicians during every visit based on an interview with the parent and child. Responders are defined as having a minimum 25% reduction in ADHD RS total score and also the change in Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) and Conners Parent Rating Scale-Revised: Short Form (CPRS-R:S)</td>
<td>Atomoxetine: Age- mean=9.7 Gender- 98(76%) male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: Age- mean=10 Gender- 103(83%) male</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/ eligible/ enrolled</th>
<th>Number withdrawn/ lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>2002</td>
<td>Mean IQ: Atomoxetine=103, placebo=106.9, p=0.021</td>
<td>409 screened/ 291 eligible/ 253 enrolled</td>
<td>59 withdrawn/ 0 lost to fu/ 253 analyzed</td>
</tr>
</tbody>
</table>
Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>2002</td>
<td>atomoxetine: placebo = mean-study1, p value; mean-study2, p value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD RS Total = -15.6:-5.5, p&lt;0.001; -14.4:-5.9, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD RS sub--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inattentive = -7.5:-3.0, p&lt;0.001; -7.6:-3.0, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity/impulsive = -8.0:-2.5, p&lt;0.001; -6.9:-2.9, p=0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CGI-ADHD-severity = -1.2:-0.5, p=0.003; -1.5:-0.7, p=0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPRS-ADHD Index = -5.7:-2.6, p=0.023; -8.8:-2.1, p&lt;0.001</td>
</tr>
</tbody>
</table>

ADHD RS total score deduction percentage
Study1 -- atomoxetine: placebo = 64.1%: 24.6%, p<0.001
Study2 -- atomoxetine: placebo = 58.7%: 40.0%, p=0.048
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>2002</td>
<td>vital sign assessment NR for symptoms</td>
<td>Atomoxetine: placebo</td>
<td>heart rate, bmp=9.2:1.5, p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Headache, abdominal pain, rhinitis, pharyngitis, vomiting, cough increased, nervousness, somnolence, nausea: NS Decreased appetite= 21.7%: 7%, p&lt;0.05 Systolic blood pressure, temperature: NS Diastolic blood pressure= 9.6:8.3, p=0.008</td>
<td>atomoxetine: total withdrawals=27 due to adverse events=6(4.7%) placebo: total withdrawals=32 due to adverse events=3(2.4%)</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity trait: placebo n vs atomoxetine n</th>
</tr>
</thead>
</table>
| Michelson    | 2002 Fair      | RCT, DB, parallel, setting:NR | Children and adolescents, 6-16 years of age, who met DSM-IV criteria for ADHD, as assessed by clinical interview and confirmed by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)(7), were eligible to participate. All patients were required to meet a symptom severity threshold: a score at least 1.5 standard deviations above age and gender norms as assessed by the investigator-administered and -scored parent version of the ADHD Rating Scale -IV. Comorbid psychiatric conditions were assessed clinically and with the K-SADS-PL. | Oppositional defiant disorder: 21.2% vs 18.8%  
Depression: 1.2% vs 2.4%  
Generalized Anxiety Disorder: 0% vs 1.2%  
Specific Phobia: 2.4% vs 3.5%. |
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson</td>
<td>2002 Fair</td>
<td>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.</td>
<td>NR</td>
<td>5 day washout</td>
<td>Primary outcome measure was total score on ADHD Rating Scale-IV. Other outcome assessment tools included: Connor's Parent Rating Scale Revised: Short Form, Connor's Teacher Rating Scale-Revised: Short Form, CGI severity score, 13-item parent-rated diary assessing efficacy rates with a Likert scale. Laboratory exams were also conducted at baseline and endpoint.</td>
<td>children aged 6-16 years/ 70.6% male, 29.4% female/ ethnicity NR.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson</td>
<td>2002 Fair</td>
<td>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</td>
<td>NR/ 171/170</td>
<td>3%/NR/ 170</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Quality</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson</td>
<td>2002</td>
<td>Fair</td>
<td><strong>Placebo</strong> (N=83) baseline mean vs mean of change from baseline; <strong>Atomoxetine</strong> (N=84) baseline mean vs mean of change from baseline; analysis of variance p-value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADHA rating scale-IV: 36.7 vs -5; 37.6 vs -12.8; p=0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CGI severity score: 4.6 vs -0.5; 4.7 vs -1.2; p=0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conners Parent rating scale: 26.5 vs -2.4; 27 vs -7.6; p=0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Connors Teacher rating scale: 21.6 vs -1.6; 21.5 vs -5.1; p=0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parent ratings of offspring behavior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>problems with homework/tasks: 1.8 vs -0.3; 1.8 vs -0.5; p=0.49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>sitting thorough dinner: 1.0 vs -0.1; 1.3 vs -0.4; p=0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulty playing quietly: 1.4 vs -0.3; 1.5 vs -0.5; p=0.15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>inattentive and distractible: 1.8 vs -0.3; 1.9 vs -0.7; p=0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>arguing or struggling-evening: 1.4 vs -0.3; 1.5 vs -0.4; p=0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>irritability-evening: 1.3 vs -0.3; 1.6 vs -0.6; p=0.43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulty with transitions: 1.5 vs -0.3; 1.6 vs -0.6; p=0.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulty settling at bedtime: 1.7 vs -0.3; 1.8 vs -0.6; p=0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulty falling asleep: 1.6 vs -0.4; 1.8 vs -0.6; p=0.30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulty getting out of bed: 1.1 vs -0.2; 1.1 vs -0.3; p=0.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>difficulty getting ready: 1.4 vs -0.2; 1.1 vs -0.3; p=0.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>arguing or struggling-morning: 1.0 vs -0.2; 1.0 vs -0.2; p=0.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>irritability-morning: 0.8 vs -0.1; 0.8 vs -0.1; p=0.74</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson</td>
<td>2002 (Fair)</td>
<td>reports from patient/parent of negative physical symptoms</td>
<td><strong>Event</strong>: Placebo: N, % vs Atomoxetine: N, %; <strong>Fisher's Exact p</strong> &lt;br&gt; Headache: 15, 17.6% vs 17, 20.0%; 0.85 &lt;br&gt; Rhinitis: 18, 21.2% vs 14, 16.5%; 0.56 &lt;br&gt; Decreased appetite: 5, 5.9% vs 17, 20.0%; 0.02 &lt;br&gt; Abdominal pain: 7, 8.2% vs 14, 16.5%; 0.17 &lt;br&gt; Pharyngitis: 13, 15.3% vs 6, 7.1%; 0.15 &lt;br&gt; Increased coughing: 11, 12.9% vs 6, 7.1%; 0.31 &lt;br&gt; Somnolence: 6, 7.1%; 9, 10.6%; 0.59 &lt;br&gt; Vomiting: 1, 1.2% vs 13, 15.3%; 0.001 &lt;br&gt; Nausea: 2, 2.4% vs 10, 11.8%; 0.04 &lt;br&gt; Asthenia: 1, 1.2%, 9, 10.6%; 0.02 &lt;br&gt; Emotional lability: 4, 4.7%, 6, 7.1%; 0.50 &lt;br&gt; Rash: 4, 4.7%; 5, 7.1; 0.75 &lt;br&gt; Accidental injury: 4, 4.7%; 5, 5.9%; 0.99 &lt;br&gt; Fever: 3, 3.5%; 6,7.1%; 0.50 &lt;br&gt; Dyspepsia: 0, 0%; 8, 9.4%; 0.007 &lt;br&gt; Dizziness: 0, 0%; 5, 5.9%; 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 subjects/2 subjects</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson</td>
<td>RCT, DB, parallel,</td>
<td>Setting: 13 outpatient sites in the United States, Patient visits were weekly for the first 4 weeks of study, and bi-weekly for the remaining 4 weeks of study.</td>
<td>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).</td>
<td>ADHD subtypes: mixed: 67%, hyperactive/impulsive: 2%, inattentive: 31%, unspecified: less than 1%. Co-morbid conditions: oppositional/defiant disorder: 38%, depression: less than 1%, generalized anxiety disorder: less than 1%.</td>
</tr>
</tbody>
</table>
# Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson</td>
<td>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.</td>
<td>12-18 day evaluation and washout period. Sizes NR.</td>
<td>NR</td>
<td>ADHD RS (semistructured interview with patient's caregiver), Conner's Parent Rating Scale: revised: short-form, Clinical Global Impressions of Severity. Affective symptoms were assessed using Children's Depression Rating Scale. Social and family functioning assessed with Child health Questionnaire. Binary measure assessed with Fisher's exact test. Dose-response relationships assessed with Cochran-Armitage trend test.</td>
<td>mean age 11.2</td>
<td>male: 71%</td>
<td>female: 29%</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson</td>
<td>2001 Good</td>
<td></td>
<td>381/297/2</td>
<td>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.</td>
</tr>
<tr>
<td>Author</td>
<td>Year (Quality)</td>
<td>Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>---------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michelson</td>
<td>2001 (Good)</td>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD RS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total: -5.8 vs -9.9 (-8.9, 0.9) vs -13.6 (-12.1, -4.0, p&lt;0.05) vs -13.5 (-11.9, -3.7; p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inattention subscale: -2.5 vs -5.1 (-5.2, 0.3) vs -7.0 (-6.8, -2.2, p&lt;0.05) vs -6.8 (-6.6, -2.0, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyper/Imp Subscale: -3.2 vs -4.8 (-4.1, 1.0) vs -6.6 (-5.6, -1.4, p&lt;0.05) vs -6.7 (-5.7, -1.4, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPRS-R</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD Index: -1.5 vs -7.2 (-9.2, -2.1, p&lt;0.05) vs -8.9 (-10.3, -4.5, p&lt;0.05) vs -8.8 (-10.0, -4.2, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactive Subscale: -1.1 vs -4.1 (-4.5, -1.2, p&lt;0.05) vs -4.1 (-4.4, -1.6, p&lt;0.05) vs -4.3 (-4.5, -1.8, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cognitive Subscale: -0.4 vs -2.4 (-4.7, -0.6, p&lt;0.05) vs -4.8 (-6.0, -2.6, p&lt;0.05) vs -4.6 (-5.8, -2.4, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oppositional Subscale: 1.1 vs -0.3 (-4.0, 1.6) vs -1.5 (-5.0, -0.5, p&lt;0.05) vs -2.0 (-5.2, -0.7, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDQRS-R: 1.1 vs -0.3 (-4.0, 1.6) vs -1.5 (-5.0, -0.5, p&lt;0.05) vs -2.0 (-5.2, -0.7, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical: 0.4 vs -.6 (-4.1, 0.25) vs -1.1 (-4.0, 1.4) vs -2.0 (-4.9, 0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychosocial Summary Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Behavior: -0.4 vs 8.2 (1.7, 15.7, p&lt;0.05) vs 13.0 (7.9, 19.5, p&lt;0.05), 16.3 (10.9, 22.4, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family activity: 0.7 vs 8.7 (-0.6, 17.9) vs 14.6 (6.3, 21.5, p&lt;0.05), 15.2 (7.3, 22.2, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parent impact-emotional: 3.0 vs 5.7 (-6.1, 11.1) vs 10.1 (-0.3, 14.0) vs 11.0 (1.2, 15.2, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Child emotional: -4.4 vs 7.6 (-3.2, 26.1) vs 7.9 (-0.4, 23.9) vs 15.9 (7.7, 31.6, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Child mental health: -1.9 vs 7.7 (3.7, 15.1, p&lt;0.05) vs 4.5 (1.6, 11.1, p&lt;0.05) vs 8.9 (5.6, 15.0, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Child self-esteem: 1.4 vs 1.4 (-4.7, 9.3) vs 5.4 (-3, 11.9, p&lt;0.05) vs 8.4 (4.2, 15.6, p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson</td>
<td>2001 (Good)</td>
<td>The following vital signs were tracked throughout the study: Blood Pressure Systolic, Diastolic, Pulse, Weight. Patient self-reports of negative health symptoms were noted at appointments.</td>
<td>Symptom: placebo vs ATMX 0.5mg/kg/day vs ATMX 1.2mg/kg/day vs ATMX 1.8mg/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 0.</td>
<td>Less than 1% of withdrawals were due to adverse events.</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biederman 2002</td>
<td>RCT, DB</td>
<td>51 girls who met the diagnostic criteria for ADHD based on DSM-IV and as assessed by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia and with normal intelligence based on WISC, 3rd edition. Exclusionary criteria: poor metabolism of cytochrome P450 2D6 isoenzyme, weight &lt;25kg at initial visit; a documented history of bipolar I or II or of psychosis; history of organic brain disease or a seizure disorder; currently taking psychotropic medicine; history of alcohol or drug abuse in past 3 months; positive screening for drugs of abuse; or significant previous or current medical conditions (eg, HIV positive, surgically corrected congenital heart defects, leukemia in remission).</td>
<td>Oppositional/defiant disorder: 38.5% Phobias: 13.5%</td>
</tr>
<tr>
<td>Michelson 2004</td>
<td>RCT, DB</td>
<td>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</td>
<td>Atomoxetine: n=292 Comorbid condition oppositional defiant disorder: 42.1% depression: 2.1% generalized anxiety disorder: 2.7% Placebo: n=124 Comorbid condition oppositional defiant disorder: 45.2% depression: 1.6% generalized anxiety disorder: 2.4%</td>
</tr>
</tbody>
</table>
# Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author Year (Quality)</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age Gender Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biederman 2002 Subgroup Analysis of Girls from Michelson 2001</td>
<td>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)</td>
<td>2-week washout, screening, and assessment period</td>
<td>No</td>
<td>Primary efficacy measure: ADHD Rating Scale - IV-Parent Version (ADHD RS), an 18-item scale. Secondary measures: Conners' Parent Rating Scale-Revised: Short Form (CPRS-R) and the Clinical Glocal Impressions of ADHD Severity (CGI-ADHD-S). The ADHD RS was given at every weekly visit (it assessed the severity of symptoms in the previous week) to parents.</td>
<td>Mean age in years: 9.66 Males = 0% Ethnicity = NR</td>
</tr>
<tr>
<td>Michelson 2004 2004</td>
<td>Atomoxetine 1.2mg/kg/day-1.8mg/kg/day for the first 10 weeks then atomoxetine or placebo for 9 months</td>
<td>NR</td>
<td>NR</td>
<td>ADHD RS and Clinical Global Impressions of Severity (CGI-S): primary assessments, bi-weekly. Child Health Questionnaire, Children's Depression Rating Scale, Conners Parent Rating Scale-Revised: Short, Conners Teacher Rating Scale-Revised: Short, WISC-III, and the Multidimensional Anxiety Scale.</td>
<td>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</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biederman 2002</td>
<td>Subgroup Analysis of Girls from Michelson 2001</td>
<td>Diagnostic subtypes:</td>
<td>NR/NR/291 (52 total girls)</td>
<td>1/NR/51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Inattentive = 21.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hyperactive/Impulsive = 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Combined = 78.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Scores:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>WISC Full Scale IQ = 105.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD RS Total T-Score = 88.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD RS (Total) = 38.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD RS Inattentive subscale = 21.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD RS Hyperactive/Impulsive subscale = 16.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPRS-R ADHD index = 26.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CGI-ADHD-S = 4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michelson 2004</td>
<td></td>
<td>Atomoxetine: n=292</td>
<td>NR/NR/60</td>
<td>10/NR/414</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>ADHD subtype</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>combined: 72.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>hyperactivity/Impulsive: 4.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inattentive: 22.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Previous stimulant treatment: 53.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo: n=124</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>combined: 74.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>hyperactivity/Impulsive: 4.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inattentive: 21.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Previous stimulant treatment: 50.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biederman</td>
<td>2002 Subgroup Analysis of Girls from Michelson 2001</td>
<td>ADHD RS Total score decrease - Atomoxetine-treated vs. placebo: -15.8 vs. -5.8, p=0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD RS Inattentive subscale decrease - Atomoxetine-treated vs. placebo: -8.8 vs. -3.4, p=0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD RS Hyperactivity/Impulsive subscale decrease - Atomoxetine-treated vs. placebo: -7.0 vs. -2.3 p=0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A visit-wise analysis found that atomoxetine-treated patients experienced significant efficacy over placebo that was evident every week of treatment (p&lt;0.05 for Weeks 1, 2, 5, and 6; p&lt;0.01 for Weeks 3, 4, 7, 8, and 9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPRS-R ADHD Index scores decrease - Atomoxetine-treated vs. placebo: -10.3 vs. -1.0, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CGI-ADHD-S score decrease - Atomoxetine-treated vs. placebo: -1.5 vs. -0.6, p&lt;0.001</td>
</tr>
<tr>
<td>Michelson</td>
<td>2004</td>
<td>Survival curve, proportion not relapsing: atomoxetine&gt;placebo, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atomoxetine baseline: change from baseline vs. placebo baseline: change from baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD RS - 15.8: 6.8 vs 15.7: 12.3, p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CGI-S score - 2.3: 0.9 vs 2.2: 1.4, p=0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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&lt;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&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CTRS - all NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHQ - 43.4: -5.6 vs 44.0: -9.5, p=0.016</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biederman 2002</strong></td>
<td>AE's reported by patients</td>
<td>Placebo (n=21)*</td>
<td>3 withdrawals/ 2 due to AE's</td>
<td></td>
</tr>
<tr>
<td><strong>Subgroup Analysis of Girls from Michelson 2001</strong></td>
<td></td>
<td>Rhinitis 25.8% 38.1%</td>
<td></td>
<td><em>(no statistically significant differences between these two groups)</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal pain 29.0% 14.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headache 25.8% 14.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pharyngitis 19.4% 19.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased appetite 19.4% 19.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting 19.4% 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cough increased 16.1% 4.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nervousness 6.5% 14.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Somnolence 6.5% 14.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea 6.5% 14.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emotional lability 3.2% 14.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever 9.7% 4.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia 3.2% 9.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhea 3.2% 4.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness 3.2% 4.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Michelson 2004</strong></td>
<td>Self-report</td>
<td>Atom.(n=31)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atomoxetine: placebo</td>
<td></td>
<td>atomoxetine:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>number of adverse events- 191(65.6%): 9(3.1%):</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>66(53.7%), p=0.027</td>
<td></td>
<td>placebo:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mean weight gain- 1.2: 3.3, p&lt;0.001</td>
<td></td>
<td>1(0.8%):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mean height gain- 2.5: 2.9, p=0.088</td>
<td></td>
<td>p=0.293</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS in routine chemistry, liver function tests, hematological measures, or cardiac QT intervals(corrected for heart rate)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Poor</td>
<td>RCT, DB, parallel. Setting: one center in a four-center study</td>
<td>Children aged 6-12 years meeting DSM-III criteria for ADD-H and scoring &gt;1.5 on the hyperactive factor the for the teacher's Conners questionnaire and &gt;1.5 on the impulsive-hyperactive or restless--immature factors for the parent's Conners questionnaire. Required to weigh &lt; 20 kg, be in good physical health, and to have normal hematological and clinical lab values as well as a normal EEG and EKG.</td>
<td>Conduct Disorder: 1 (10%) in placebo group, 0 in bupropion group</td>
</tr>
<tr>
<td>Casat, 1987</td>
<td></td>
<td>RCT, DB, parallel. Setting: one center in a four-center study</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Setting: one center in a four-center study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connors</td>
<td>Fair</td>
<td>RCT, DB, parallel. Setting: one inpatient treatment facility (n=6), rest from one out-patient university psychiatry clinic. Doctors and researches tracked a weekly log of drug administering completed by parent of patients. 6 week study.</td>
<td>Children aged 6-12 years meeting DSM-III criteria for ADDH.</td>
<td>NR</td>
</tr>
<tr>
<td>1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age and Gender/Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casat, 1987</td>
<td>Bupropion hydrochloride 50mg and 75mg tabs with escalated doses based on weight (20-30kg, 30-40kg, and &gt;40kg). Days 1-3 dose was 3mg/kg, escalated to 6mg/kg for days 15-28 with a maximum dose for the low weight group being 150mg/day, the middle weight group being 200mg/day and the high weight group being 250mg/day. OR Placebo. Administered twice a day at 7am and 7pm. This is a 6 week study.</td>
<td>SB 1 week placebo run-in</td>
<td>None</td>
<td>Brief Psychiatric Rating Scale for Children (BPRS-C); the Beitchman Children's Self-Report Psychiatric Rating Scale; the 93-item Conners Parent Symptom Questionnaire (CPSQ) and 39-item Conners Teacher Questionnaire (CTQ); and the abbreviated 10-item Conners Parent-Teacher Questionnaire. Physical exam, hematological and clinical labs, EEG, and EKG. Computerized versions of the short-term memory task (STMT) and continuous performance task (CPT). Timing NR</td>
<td>Mean age: bupropion=9.0 (6.8-11.5), placebo=8.4 (6.3-12.4) Males: 25 (83%) White: 24 (80%)</td>
</tr>
<tr>
<td>Connors, 1996</td>
<td>Bupropion 3-6mg/kg/day or placebo, administered twice daily, at 7am and 7pm. This was a 6 week study.</td>
<td>1 week, single-blind washout.</td>
<td>NR</td>
<td>Connors parent Questionnaire, Connors Teacher questionnaire, Clinical Global Impressions-Severity Scale, Short-Term memory Test, Continuous performance Test, Physical examination, laboratory battery.</td>
<td>Mean age 8.5 years. Males: 90% Females: 10%. Caucasian: 75%, Non-Caucasian: 25%</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupriopion</td>
<td>Casat, 1987</td>
<td>NR</td>
<td>NR/31/30</td>
<td>2/0/30</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>(Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casat, 1987</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Statistically significant differences between treatment groups over time:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical Global Impressions Scale:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severity: F=2.34, p=0.026</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improvement: F=2.61, p=0.019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CTQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity: F=4.98, p=0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Differences between treatment groups over time that are not statistically significant:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPSQ-Hyperactivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPSQ-Conduct</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CTQ-Conduct</td>
</tr>
</tbody>
</table>

## Connors 1996

### Bupropion vs placebo

|                           | Parent (observed mean scores at 28 days) (n=62 vs n=34): 13.81 vs 16.91, p-value NR; |
|---------------------------| (our calculation of mean change: -5.74 vs -3.76) |
|                           | Teacher (observed mean scores at 28 days) (n=54 vs n=27): 14.67 vs 19.11, p-value NR; |
|                           | (our calculation of mean change: -5.36 vs -1.47) |
|                           | ANCOVA results (probability values for Treatment; Treatmentxday) |
| 10-Item form (LOCF)--     | Teacher: 0.0003, NS; Parent: NS, NS |
| 10-Item form (observed)-- | Teacher: 0.001, NS; Parent: NS, NS |
| 39-Item Teacher Form (LOCF)-- | Conduct Disorder: 0.05; NS; Hyperactivity: 0.08; NS |
| 39-Item Teacher Form (observed)-- | Conduct Disorder: 0.02, NS; Hyperactivity: 0.03, NS |
| 93-Item Parent Form (LOCF)-- | Conduct Disorder :NS, 0.01; Restless-Impulsive: NS, 0.01; Hyperactive-Immature: 0.06, NS |
| 93-Item Parent Form (observed)-- | Conduct Disorder: 0.09, 0.017; Restless-Impulsive: 0.096, 0.013; Hyperactive-Immature: 0.02, NS |
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Casat</td>
<td>Physical exam, hematological and clinical labs, EEG, and EKG.</td>
<td>1 (3%) subject had rash, perioral edema and agitation</td>
<td></td>
<td>2 withdrawals (1 in placebo group no reason given at day 17 and 1 in bupropion group for rash, perioral edema and agitation at day 18)</td>
</tr>
<tr>
<td></td>
<td>1987</td>
<td>Height and weight taken at visits.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>Other means of reporting adverse effects was NR.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connors</td>
<td>1996</td>
<td>Report from patient/patient's parent of negative symptoms.</td>
<td>No statistically significant effects on height, weight, blood pressure.</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Study Design</td>
<td>Setting</td>
<td>Eligibility criteria</td>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>--------------</td>
<td>---------</td>
<td>----------------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td>Daviss 2001 United States Poor</td>
<td>CCT Open-label Single Blind Setting: NR</td>
<td>Adolescent patients aged 11 to 18 years who met DSM-IV criteria for any subtype of ADHD and comorbid MDD or DD were eligible to participate. At least one parent and one teacher rating of sufficient ADHD symptomatology (≥ 6 inattentive or 6 hyperactive-impulsive symptoms rated &quot;often&quot; or &quot;very often&quot; on ARS; ≥ 6 inattentive or 6 hyperactive-impulsive symptoms rated &quot;pretty much&quot; or &quot;very much&quot; on SNAP; Attention problems T score ≥ 67 on CBCL or TRF). At least one parent OR one child rating of sufficient depressive symptomatology (Parent MFQ score ≥ 20; Child MFQ score ≥ 25; CBCL or YSR Anxious/Depressed T score ≥ 67). Psychiatrist ratings of sufficient clinical severity [CGI Severity for ADHD ≥ 4 (&quot;moderate&quot;), CGI Severity for depression ≥ 4 (&quot;moderate&quot;)</td>
<td>Additional diagnoses: ODD=50% Specific phobia=25% Social phobia=21% Conduct disorder=21% Generalized anxiety disorder=17% Posttraumatic stress disorder=17% Panic disorder without agoraphobia=4% Separation anxiety disorder=4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age (Gender, Ethnicity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daviss</td>
<td>2-week single-blind placebo lead-in</td>
<td>2-week washout before</td>
<td>NR</td>
<td>Swanson, Nolan, and Pelham (SNAP) scale</td>
<td>Mean age=12.8 (75% male, 100% white)</td>
</tr>
<tr>
<td>2001 United States</td>
<td>Buproprion vs Placebo</td>
<td>enrollment; then 2-week single-blind placebo lead-in</td>
<td></td>
<td>Child Behavior Checklist (CBCL) Teacher's Report Form (TRF) ADHD Rating Scale Mood and Feelings Questionnaire (C-MFQ and P-MFQ)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>THEN: Step 1 (visits 1 and 2): morning doses not exceeding 2 mg/kg and 100 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thereafter (anytime during visits 3-5) Step 2: up to 3 mg/kg qAM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Step 3: up to 3 mg/kg qAM and 2 mg/kg at 5 PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Step 4: up to 3 mg/kg qAM and 3 mg/kg at 5 PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: up to 10 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daviss</td>
<td>2001 United States Poor</td>
<td>NR/NR/25</td>
<td>4 (16%) withdrawn/0 lost to fu/analyzed=24</td>
</tr>
</tbody>
</table>

**Other population characteristics (mean scores)**

- Primary diagnosis:
  - ADHD, combined type=58%
  - ADHD, inattentive type=42%
  - MDD+DD=63%
  - DD alone=29%
  - MDD alone=8%

- Previous medications tried:
  - At least one stimulant=50%
  - At least one SSRI=25%
  - Venlafaxine=8%
  - Bupropion IR=4%
  - Clonidine=4%
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daviss</td>
<td>2001 Poor</td>
<td>Bupropion SR vs placebo: visit 2 (end of placebo period)/final visit; Paired t Test, p-value (compares visit 2 and final visit)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P-ARS: 28.3/17.4; 5.13, p&lt;0.0005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T-ARS: 28.7/23.7; 1.84, p=NS</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td>P-MFQ: 21.6/10.0; 4.93, p&lt;0.0005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C-MFQ: 13.6/8.5; 2.60, p=0.016</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>P-CIS: 30.4(visit 1)/18.3; 4.96, p&lt;0.0005</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daviss</td>
<td>2001 United States Poor</td>
<td>NR</td>
<td>Bupropion vs placebo in run-in phase</td>
<td>Total withdrawals: 3 (12.5%) vs 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Headaches=8% vs 8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fatigue=4% vs 4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nausea=8% vs 13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rash=13% vs 4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Insomnia=4% vs 4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Irritability=8% vs 4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tremor=4% vs 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Motor tics=4% vs 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Design</td>
<td>Setting</td>
<td>Eligibility criteria</td>
<td>Comorbidity</td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Clonidine</td>
<td></td>
<td>RCT, DB, setting: john Hopkins Tourette Syndrome Clinic</td>
<td>Children with both Tourette's Syndrome and ADHD.</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Singer</td>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singer</td>
<td>each child started with 1 capsule per day, and added 1 capsule every week to a maximum daily dose of 1 capsule</td>
<td>1 week washout between clonidine and desipramine</td>
<td>NR/ NR</td>
<td>The Child Behavior Checklist (CBCL), Gordon Diagnostic System, Clinical Evaluation of Language Function, Matching Familial Figures Test, Porteus Maze test, Restricted Academic Test, Global Linear Analogue, Tourette Syndrome Severity Scale, Hopkins Motor/Vocal Tic Scale, Leyton Obsessional Inventory-Child Version</td>
<td>children ages 7.2-13.6 years/ 31 male and 3 female/ 33 Caucasian and 1 African-American</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singer 1995</td>
<td></td>
<td>NR</td>
<td>48/37/34</td>
<td>3/1/1934</td>
</tr>
</tbody>
</table>

Fair
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>(Quality)</th>
<th><strong>Clonidine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Singer</td>
<td>1995</td>
<td>Fair</td>
<td><strong>End-of-treatment Values</strong>: group means +/- SD: clonidine vs desipramine vs placebo</td>
</tr>
</tbody>
</table>

#### 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
- **Hyperactivity (boys 6-11yrs) (M)**: 70.7 +/- 1.2 vs 68.6 +/- 1.4 vs 75.8 +/- 1.0
- **Nervous/overactive (boys 6-11yrs) (T)**: 63.7 +/- 0.5 vs 61.9 +/- 0.2 vs 69.6 +/- 0.2
- **Unpopular (boys>12y) (T)**: 59.0 +/- 0.8 vs 60.4 +/- 0.8 vs 65.8 +/- 1.8
- **Anxious (boys>12yrs) (T)**: 58.0 +/- 1.2 vs 56.0 +/- 0.2 vs 60.9 +/- 2.5
- **Obsessive-compulsive (boys>12 yrs) (T)**: 65.7 +/- 3.4 vs 60.4 +/- 0.9 vs 66.9 +/- 3.3

#### Analysis of Variance for Significant Attention-Deficit Hyperactivity Disorder Variables and Drug Orthogonal Contrasts, Source: Df vs FValue vs Probability > FValue

- **Parent linear "hyperactivity" analogue (n=34)**:
  - Drug effect: 2 vs 13.06 vs .001; Desipramine vs clonidine: 1 vs 25.26 vs .001
  - Order effect: 2 vs 3.62 vs .03; Drug X Order effect: 4 vs 1.15 vs NS

- **Mother CBCL "hyperactivity", boys 6-11 yrs (n=23)**:
  - Drug effect: 2 vs 4.08 vs .02; Desipramine vs clonidine: 1 vs 8.04 vs .006
  - Order effect: 2 vs 0.99 vs NS; Drug X Order effect: 4 vs 4.47 vs .003

- **Teacher CBCL "nervous/overactive", boys 6-1 yrs (n=23)**:
  - Drug effect: 2 vs 4.52 vs .02; Desipramine vs clonidine: 1 vs 8.65 vs .005
  - Order effect: 2 vs 0.45 vs NS; Drug X Order effect: 4 vs 0.48 vs NS

- **Teacher CBCL "unpopular", boys>12 yrs (n=8)**:
  - Drug effect: 2 vs 4.91 vs .02; Desipramine vs clonidine: 1 vs 5.29 vs .04
  - Order effect: 2 vs 1.10 vs NS; Drug X Order effect: 4 vs 1.15 vs NS

- **Teacher CBCL "anxious" boys>12 y (n=8)**:
  - Drug effect: 2 vs 8.97 vs .002; Desipramine vs clonidine: 1 vs 16.62 vs .001
  - Order effect: 2 vs 11.07 vs .001; Drug X Order effect: 4 vs 6.08 vs .004

#### Analysis of Variance for Significant Tic and Obsessive-Compulsive Variables and Drug Orthogonal Contrasts

- **Parent linear analogue for tics (n=24)**:
  - Drug effect: 2 vs 3.73 vs .03; Desipramine vs clonidine: 1 vs 6.65 vs .01; Order effect: 2 vs 1.30 vs NS; Drug X order effect: 4 vs 1.70 vs NS;

- **Teacher CBCL "obsessive-compulsive", boys>12 y (n=8)**:
  - Drug effect: 2 vs 6.02 vs .01; Desipramine vs clonidine: 1 vs 11.28 vs .004; Order effect: 2 vs 11.95 vs .001; Drug X order effect: 4 vs 7.15 vs .002
<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singer</td>
<td>report from patients of negative physical symptoms</td>
<td>clinicians were unable to correlate drug-related adverse symptoms to clonidine or desipramine. &quot;To date, at least 4 sudden, unexplainable deaths have occurred in children receiving this (Desipramine) medication.&quot;</td>
<td>NR;NR</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunt</td>
<td>1986</td>
<td>RCT, double-blind, parallel. Setting:NR</td>
<td>NR</td>
<td>A child had to meet DSM-III criteria for ADD-H and score at least 2.0 standard deviation (s.d.) above normal on the Hyperactivity Index of the Connors Behavior Rating Scale (C-BRS) as rated by either parent or teacher. All subjects had an IQ greater than 80 and had no symptom of psychosis or primary mood disturbance. All were medically healthy with no cardiac, endocrine, or neurological disorder.</td>
<td>100% receiving special education services, 70% had been previously treated with stimulant medication for ADHD</td>
</tr>
<tr>
<td>Hunt</td>
<td>1985</td>
<td>Poor</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pharmacologic Treatments for ADHD Page 296 of 616
**Evidence Table 5. Placebo-controlled trials in children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunt 1986</td>
<td>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).</td>
<td>NR</td>
<td>NR/ no other types of interventions used.</td>
<td>Connors Behavioral Ratings given by clinicians, Connors 28-Item scale for Teacher's ratings, Connors 48-Item scale for Parent's ratings, Videotaped observations done monthly, Neuromaturational assessment conducted monthly, Digit Span to test auditory attention, Kagen Matching Familiar Figures Test to measure impulsivity, visual scanning and frustration tolerance-all done by clinicians.</td>
<td>10 children age mean 11.6 years. Gender, ethnicity, etc NR.</td>
</tr>
<tr>
<td>Hunt 1985</td>
<td>baseline, and 2 weeks back to placebo (12 week study altogether).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunt</td>
<td>NR</td>
<td>NR/NR/10</td>
<td>0/0/n=10</td>
</tr>
<tr>
<td>1986</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hunt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunt</td>
<td>1986</td>
<td>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.</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>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)</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunt</td>
<td>1986</td>
<td>reports from teachers, parents, clinicians. Blood pressure monitored.</td>
<td>90% (9 children) reported sleepiness in first hour after dose. Mean blood pressure decreased 10% on clonidine.</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Hunt</td>
<td>1985</td>
<td>10% (1 child) reported increased depressive symptoms on clonidine.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td>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)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scahill</td>
<td>2001 United States</td>
<td>RCT, DB, Parallel groups</td>
<td>Patients recruited from Tic Disorders Clinic of the Yale Child Study Center Age between 7 and 15 years, a DSM-IV diagnosis of ADHD (any type), a DSM-IV tic disorder (any type), and a score of ≥ 1.5 SDs for age and gender of the 10-item Conners hyperactivity index rated by the teacher or a parent; enrollment in the same school for at least a month before entry, with no planned change in school placements for at least 10 weeks after entry</td>
<td>DSM-IV tic disorders Tourette's: 20 (58.8%) Chronic motor tic disorder: 12 (35.3%)</td>
</tr>
</tbody>
</table>
**Evidence Table 5. Placebo-controlled trials in children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Duration</th>
<th>Dosing schedule</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scahill</td>
<td>2001</td>
<td>United States</td>
<td>Guanfacine vs placebo</td>
<td>Placebo washout of 7-14 days</td>
<td>NR</td>
<td>ADHD Rating Scale</td>
<td>Mean age=10.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days 1-3: single 0.5 mg dose at bedtime</td>
<td></td>
<td></td>
<td>Clinical Global Impression global improvement score</td>
<td>91.2% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days 4-7: 0.5 mg doses in the morning and at bedtime (TDD=1.0 mg)</td>
<td></td>
<td></td>
<td>Hyperactivity index of the Parent Conners Questionnaire</td>
<td>85.3% White</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days 8-14: 0.5 mg doses in the morning, afternoon and bedtime (TDD=1.5 mg)</td>
<td></td>
<td></td>
<td>Yale Global Tic Severity Scale</td>
<td>0.6% Black</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Days 15-28: upward adjustment to a maximum allowable dose of 4 mg/day (TID)</td>
<td></td>
<td></td>
<td>Children's Yale-Brown Obsessive Compulsive Scale</td>
<td>0.6% Hispanic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Continuous Performance Test</td>
<td>0.3% Asian</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Duration=8 weeks</td>
<td></td>
</tr>
</tbody>
</table>

- **Method of Outcome Assessment and Timing of Assessment**:
  - ADHD Rating Scale
  - Clinical Global Impression global improvement score
  - Hyperactivity index of the Parent Conners Questionnaire
  - Yale Global Tic Severity Scale
  - Children's Yale-Brown Obsessive Compulsive Scale
  - Continuous Performance Test
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guanfacine</td>
<td>Scahill</td>
<td>ADHD Rating Scale score=35.8&lt;br&gt;Parent Conners Questionnaire hyperactivity index score=17.6&lt;br&gt;Yale Global Tic Severity Scale Total Score=15.3&lt;br&gt;Body Weight=86.1 lb</td>
<td>50/40/34</td>
<td>NR/NR/34</td>
</tr>
</tbody>
</table>
**Evidence Table 5. Placebo-controlled trials in children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guanfacine</td>
<td>2001 United States Fair</td>
<td>Guanfacine vs placebo ADHD Rating Scale Total Score-teacher (% mean change): -37% vs -8%, <em>p&lt;0.001</em> % patients with ratings of &quot;much improved&quot; or &quot;very much improved&quot; on CGI-I for clinical-rated change in ADHD symptoms: 9 (52.9%) vs 0, <em>p&lt;0.001</em> Total tic score of the Yale Global Tic Severity Scale (% mean change): -31% vs 0%, <em>p=0.05</em> Parent-rated hyperactivity index (% mean change): -27% vs -21%, <em>p=NS</em> CPT Commission errors (% mean change): -22% vs +29%, <em>p=0.01</em> Omission errors (% mean change): -17% vs +31%, <em>p=0.04</em> ADHD rating scale-teacher (endpoint means, t-score, and <em>p</em>-value for comparison of endpoint means) Inattention score: 12.8 vs 15.4, <em>t=3.79, p&lt;0.01</em> Hyperactive/impulsive score: 10.8 vs 16.3, <em>t=2.98, p&lt;0.01</em></td>
</tr>
<tr>
<td>Author</td>
<td>Year (Quality)</td>
<td>Method of adverse effects assessment</td>
</tr>
<tr>
<td>----------</td>
<td>---------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Scahill</td>
<td>2001 United States Fair</td>
<td>Modified version of the Systematic Assessment for Treatment of Emergent Events (SAFTEE)</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH ER (Metadate®)</td>
<td></td>
<td>RCT, DB (randomized 1:1 to MPH MR vs. placebo)</td>
<td>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. Exclusion criteria: comorbid psychiatric diagnosis; history of seizure, tic disorder, or family history of Tourette's syndrome; female having undergone menarche; use of amphetamines, pemoline, or an investigational drug within 30 days of study entry; concomitant use of clonidine, anticonvulsant drugs, or medications known to affect blood pressure, heart rate, or central nervous system function; hyperthyroidism or glaucoma; any concurrent chronic or acute illness (eg, allergic rhinitis, severe cold) or disability that could confound the study results. Also excluded were children who had failed a previous trial of stimulants for ADHD, had required a third daily dose in the afte</td>
<td>None reported</td>
</tr>
</tbody>
</table>
Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenhill 2002</td>
<td>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.</td>
<td>1-week, single-blind run-in period with placebo. 45 (n=24%) of children screened were found to be placebo-responders and were disqualified.</td>
<td>No</td>
<td>Primary efficacy measure: Conners' Teachers Global Index (10 items), completed by phone interview in the morning (~10am) and afternoon (~2 pm) of three alternating days of each treatment week. Secondary efficacy measures: Conners' Parent Global Index (10 item) completed on 1 day of each weekend during the morning, afternoon, and evening. Parents were also asked to complete a global assessment at the final visit, using a diary of observations they had kept during the run-in placebo week.</td>
<td>Mean age = 9 years Male = 81.8% White = 81.4% African American = 15.3% Hispanic = 10.2% Other = 3.5%</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean age = 9 years Male = 81.8% White = 81.4% African American = 15.3% Hispanic = 10.2% Other = 3.5%
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/ eligible/ enrolled</th>
<th>Number withdrawn/ lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH ER (Metadate®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenhill</td>
<td>2002 Fair</td>
<td>Previously treated for ADHD = 64.0% (n=201)</td>
<td>507 screened/ 321 eligible/ 314 analyzed</td>
<td>45 withdrawn (n=28 from placebo, n=17 from MPH MR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Conners' Global Index - Teacher = 12.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean Conners' Global Index - Parent = 13.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean CGI Severity of Disorder = 4.45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenhill</td>
<td>2002 (Fair)</td>
<td>At endpoint, investigators rated 64% of children as moderately or markedly improved with MPH MR treatment, compared with 27% of the placebo group.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conners' Global Index - Teacher's Scores (MPH MR vs. placebo):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline mean (Standard deviation): 12.7 (7.2) vs. 11.5 (7.35) (p=0.1309)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 1 mean (SD): 7.3 (4.93) vs. 10.9 (6.56) (p=0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 2 mean (SD): 5.8 (4.71) vs. 10.4 (6.75) (p=0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 3 mean (SD): 4.7 (4.77) vs. 9.2 (6.30) (p=0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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&lt;0.001).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effect size (calculated from teacher assessment) = 0.78 for MPH MR vs. placebo during last week of treatment.</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>Conners' global index - Teacher's scores (MPH MR vs. placebo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline mean (Standard deviation): 13.6 (6.6) vs. 12.9 (7.6) (p=NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weeks 1 and 2: data not specified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week 3 mean (SD): 7.4 (5.9) vs. 10.1 (6.7) (p=NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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&lt;0.001).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effect size (calculated from parent assessment) = 0.4 for MPH MR vs. placebo during last week of treatment.</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenhill</td>
<td>2002</td>
<td>Reported and observed AE's.</td>
<td>Any Adverse Event (AE) reported: Headache: 14.8% (n=23) in MPH MR; 10.6% (n=17) in placebo</td>
<td>45 withdrawals; 2 withdrawals due to adverse events</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vital signs were collected at baseline and weekly thereafter.</td>
<td>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]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parents completed the Pittsburgh 11-item side effect questionnaire the same day they completed the Conners' Global Index. Teachers also filled out a similar side effect questionnaire 3 times per week near the end of the school day, on the same days they filled out the Conners' Global Index.</td>
<td>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 &gt;=5% in either treatment group)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AE's determined by investigator to be related to study medicine: 32.9% of MPH MR and 17.4% of placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Of the two withdrawals due to AE's, one child developed a pruritic, nonerythematosus, 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.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Evidence Table 5. Placebo-controlled trials in children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rugino</td>
<td>2003</td>
<td>RCT, DB, Parallel groups</td>
<td>Regional development center</td>
<td>(1) reliable transportation to and from the development center; (2) regular school attendance; (3) an average Conners Teacher ADHD Rating Scale 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</td>
<td>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%</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rugino</td>
<td>2003 Fair</td>
<td>Modafinil mean dose=264 mg</td>
<td>NR/NR</td>
<td>NR</td>
<td>Test of Variables of Attention (TOVA)</td>
<td>Mean age=7.9</td>
<td>62.5% male</td>
<td>100% white</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td>ADHD Rating Scale IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flexible dosing</td>
<td></td>
<td></td>
<td>Conners’ Parents Ratings Scales Revised-L (CPRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dosing schedule=once each morning</td>
<td></td>
<td></td>
<td>Conners’ Teachers Rating Scales Revised-L (CTRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean study duration=5.6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>(Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
</table>
| Modafanil | Rugino | 2003 | ADHD type  
Combined=72.7%  
Inattentive=18.2%  
Hyperactive-impulsive=4.5% | NR/NR/24 | 2 (8.3%) withdrawn/0 lost to fu/analyzed=22 (modafinil=11, placebo=11) |
<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modafanil</td>
<td>Rugino 2003</td>
<td>Modafinil vs placebo (t scores representing post-treatment improvement)</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
<td>DSM-IV symptoms (CTRS and CPRS): 68.2 vs 76, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other Conners ADHD Scales (% of 14 scales with mean t score difference more negative than -5): 13 (92.8%) vs 1 (7.1%), p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD Rating Scale raw scores: 14 vs 14.7, p=NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% parents rating &quot;significant&quot; overall improvement: 10 (90.9%) vs 8 (72.7%), p&lt;0.004</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modafanil</td>
<td>Rugino 2003 Fair</td>
<td>NR</td>
<td>Delayed sleep onset: 4 (36.4%) vs 4 (36.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Modafinil (n=11)</td>
<td>Transient stomachache=2 (18.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasional transient headache=1 (9.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transient mood disorder with tearfulness=1 (9.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (n=11)</td>
<td>Sleepiness=1 (9.1%)</td>
<td>Total withdrawals: 2/13 (15.4%) vs 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irritability=1 (9.1%)</td>
<td>Withdrawals due to adverse events: nr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased appetite=1 (9.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tonsillitis/pharyngitis=1 (9.1%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross-Tsur</td>
<td>Between testing sessions: Open, unblinded, uncontrolled intervention</td>
<td>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).</td>
<td>Epilepsy</td>
</tr>
<tr>
<td>1997</td>
<td>During testing sessions: DB, single-dose crossover of methylphenidate and placebo (1/2 of children received placebo during the first testing session, and 1/2 during the second)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross-Tsur</td>
<td>First 8 weeks: antiepileptic drugs (AEDs)</td>
<td>NR/NR</td>
<td>NR</td>
<td>(1) neurologic examination</td>
<td>Mean age=9.8</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Second 8 weeks: AEDs+methylphenidate 0.3 mg/kg (observational study)</td>
<td></td>
<td></td>
<td>(2) electroencephalography</td>
<td>18 (60%) male</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>1997</td>
<td></td>
<td></td>
<td></td>
<td>(3) AED trough level and 2 hours after dosing with AED and with methylphenidate or placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td></td>
<td></td>
<td></td>
<td>(4) CPT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testing session #1 (after first eight weeks): assigned to a single dose of either methylphenidate 0.3 mg/kg or placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testing session #2 (after second eight weeks): crossed over to a single dose of either methylphenidate 0.3 mg/kg or placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean age=9.8</td>
<td></td>
<td></td>
<td></td>
<td>9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 (60%) male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ethnicity NR</td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>(Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross-Tsur</td>
<td>1997</td>
<td>Poor</td>
<td>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%)</td>
<td>NR/NR/30</td>
<td>NR/NR/30 for all but AED drug levels (n=27)</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>(Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross-Tsur</td>
<td>1997</td>
<td>Israel</td>
<td>Speed of response: MPH &gt; placebo [F(1, 30) = 10.1 (p &lt; 0.003)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor</td>
<td>Performance decrement over time: less pronounced with MPH [interaction time-on-task by drug condition was F(2, 60) = 3.8 (P &lt; 0.03)]</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross-Tsur</td>
<td>NR</td>
<td>AE's reported only for the observational study periods.</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Quality)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subgroup: Comorbidity: Epilepsy
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sverd</td>
<td>1992</td>
<td>RCT DB crossover</td>
<td>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.</td>
<td>100% ADHD and either chronic motor tic disorder or Tourette disorder</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tourette disorder: definite=7(63.6%), by history=3(27.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chronic motor tic disorder:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>definite=1(9.1%)</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sverd</td>
<td>methylphenidate (MPH): placebo, 0.1mg/kg, 0.3mg/kg, and 0.5mg/kg, bid, for 2 weeks each.</td>
<td>at least 1 week for stimulants and 3 weeks for neuroleptic (pimozide)</td>
<td>NR</td>
<td>Physician evaluation: Yale Global Tic Severity Scale (YGTSS) and Tourette Syndrome Unified Rating Scale (TS unified RS)</td>
<td>Mean age=8.3(1.96), range 6.1-11.9 years.</td>
<td>Gender=11(100%) male</td>
<td>Race: NR</td>
</tr>
<tr>
<td>1992</td>
<td>* for any given 0.1mg/kg dose, the minimum=2.5mg, the maximum=20mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Subgroup</th>
<th>Comorbidity: Tourette's Disorder</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sverd</td>
<td>1992 Fair</td>
<td>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</td>
<td>NR/ NR/ 11 enrolled</td>
<td>0/0/0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Global Severity Scores: mean=40.6(16.6), range 16-79</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Subgroup</th>
<th>Comorbidity: Tourette's Disorder</th>
<th>Results</th>
</tr>
</thead>
</table>
| Sverd  | 1992 Fair     | Placebo  | Placebo vs. 0.1mg/kg; Placebo vs. 0.3mg/kg; Placebo vs. 0.5mg/kg | Physician evaluation--  
  a. YGTSS: NS  
  b. TS unified RS: NS  
 Observations--  
  a. % ontask: p<0.01; p<0.01; p<0.01  
  b. worksheets no. of completed: p<0.05; p<0.05; p<0.01  
 Parent rating--  
  a. APRS: p<0.01; NS; p<0.05  
  b. PSSC: NS  
  c. GTRS: NS  
  d. Peer Conflict Scale: p<0.05; p<0.05; p<0.05 |
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sverd</td>
<td>1992 Fair</td>
<td>Stimulant Site Effects Checklist (SSEC) by parents</td>
<td>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</td>
<td>none</td>
</tr>
</tbody>
</table>

Total withdrawals; withdrawals due to adverse events
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varley</td>
<td>1982</td>
<td>Outpatient, randomized, DB,</td>
<td>Children with mild mental retardation (IQ was between 49 and 77), without psychotic disorders or undersocialized aggressive conduct disorders, with clinical assessment consistent with DSM-III criteria for ADD</td>
<td>Mental Retardation (mild) (100%)</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>placebo cross-over study</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varley</td>
<td>1982</td>
<td>MPH and placebo were in identical capsules.</td>
<td>None</td>
<td>NR</td>
<td>Parents and teachers kept daily rating of children's behavior while on the study; no cognitive and learning measures assessed. Teachers filled out the Conners' Teachers Questionnaire, and the parents filled out the Conners' Parent Questionnaire.</td>
<td>Median age = 11.33 (age range: 4.58 to 15 years)</td>
<td>Male = 70 %</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td>21 days; drug or placebo was administered at 8 a.m. and noon.</td>
<td>For 8 children who were MPH-naïve, doses were placebo, low =0.3 mg/kg per day, and high=0.6 mg/kg per day. 1 child taking MPH 40 mg/day had dosage of placebo, low=20 mg/ day, and high=40 mg/day. 1 child taking MPH 120 mg/day had dosage of placebo, low=60 mg/day, and high=120 mg/day.</td>
<td>Positive response was defined as significant improvement in the mean of the Conners' rating at either low or high dose compared to placebo.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median age = 11.33 (age range: 4.58 to 15 years) 
Male = 70 %
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup Comorbidity: Mental Retardation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Varley 1982 | Median IQ full score: 68 (49-77 was range)  
Social class I: 2 (20%)  
Social class III: 2 (20%)  
Social class IV: 4 (40%)  
Social class V: 2 (20%) | NR/15/10 | 0/0 |
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>(Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup</td>
<td>Comorbidity: Mental Retardation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varley</td>
<td>1982</td>
<td>Fair</td>
<td>50% showed improvement overall. Teachers'/parents' ratings on Conners' forms indicated high dosage had significantly improved (t s = 1.83/ 2.67 and p s&lt;0.05/ p s&lt;0.02) children's ADD. Low dosage had positive but non-significant trend.</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varley</td>
<td>1982</td>
<td>Parental reporting of side effects; they were given a list of common side effects. No significant side effects noted.</td>
<td>Gastrointestinal upset, nausea, decreased appetite (transient and mild) = 4 (40%) Sleeping difficulties = 2 (20%) Pulse rate increase (low dose/high dose) = +4.9 bpm/+7.2 bpm Mean Systolic blood pressure increase (low dose/high dose) = 1mm Hg/5.9 mm Hg Dyastolic blood pressure increase (low/high) = 0 mm / 3.5 mm (no subject developed an increase in either pulse or blood pressure that was greater than the normal range for their age.)</td>
<td>0/0</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadow</td>
<td>1992</td>
<td>RCT DB crossover</td>
<td>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.</td>
<td>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%)</td>
</tr>
<tr>
<td>Gadow</td>
<td>1995</td>
<td>RCT DB crossover</td>
<td>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</td>
<td>100% ADHD and either chronic motor tic disorder or Tourette disorder Tourette disorder: definite=22(64.7%), by history=12(35.3%)</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age Gender Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadow</td>
<td>1992</td>
<td>methylphenidate (MPH): placebo, 0.1mg/kg, 0.3mg/kg, and 0.5mg/kg, bid, for 2 weeks each.</td>
<td>at least 1 week for stimulants and 3 weeks for neuroleptic (pimozide)</td>
<td>NR</td>
<td>Classroom: Classroom Observation Codes Lunchroom: Code for Observing Social Activity (COSA) Playground: Code for Observing Social Activity (COSA) *Observers followed subjects while they were in the classroom, lunchroom and playground Rating Scale: Abbreviated Teacher Rating Scale, IOWA Conners Teacher's Rating Scale, Peer Conflict Scale Global Tic Rating Scale</td>
<td>Mean age=8.3(1.96), range 6.1-11.9 years. Gender=11(100%) male Race: NR</td>
</tr>
<tr>
<td>Gadow</td>
<td>1995 Fair</td>
<td>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.</td>
<td>at least 1 week for stimulants and 2 to 3 weeks for clonidine and neuroleptics</td>
<td>NR</td>
<td>Direct observations-- Classroom: Classroom Observation Codes Lunchroom: Code for Observing Social Activity (COSA) Playground: Code for Observing Social Activity (COSA) *Observers followed subjects while they were in the classroom, lunchroom and playground</td>
<td>Mean age=8.8(1.9), range 6.1-11.9 years. Gender=31(91.2%) male Race: NR</td>
</tr>
</tbody>
</table>
# Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadow</td>
<td>1992</td>
<td>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</td>
<td>NR/ NR/ 11 enrolled</td>
<td>0/0/0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Global Severity Scores: mean=40.6(16.6), range 16-79</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ADHD index: mean=8.7(1.77) Conners Hyperactivity index: mean=17.6(3.53) PSSC Hyperactivity subscale: mean=4.2(1.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadow</td>
<td>1995</td>
<td>NR</td>
<td>NR/ NR/ 34 enrolled</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Quality</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadow</td>
<td>1992</td>
<td></td>
<td>Placebo vs. 0.1mg/kg; Placebo vs. 0.3mg/kg; Placebo vs. 0.5mg/kg; 0.1mg/kg vs. 0.5mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Classroom observation--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. Interference: NS; p&lt;0.01; p&lt;0.01; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b. Motor: p&lt;0.01; p&lt;0.01; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>c. Off-task: NS; NS; p&lt;0.01; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>d. Noncompliance: p&lt;0.01; p&lt;0.01; p&lt;0.01; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lunchroom observation--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. Noncompliance: p&lt;0.05; p&lt;0.01; NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b. Physical aggression: p&lt;0.05; p&lt;0.05; p&lt;0.05; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Playground observation:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. Noncompliance: p&lt;0.05; p&lt;0.05; p&lt;0.05; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b. Physical aggression: NS; p&lt;0.05; NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rating Scales:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. ATRS: p&lt;0.01; p&lt;0.01; p&lt;0.01; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b. IOWA l-O: p&lt;0.01; p&lt;0.01; p&lt;0.01; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>c. IOWA A: p&lt;0.01; p&lt;0.01; p&lt;0.01; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>d. Peer Conflict: NS; NS; p&lt;0.01; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>In classroom, vocal tics were significantly less frequent (p&lt;0.01) on the 0.3mg/kg and the 0.5mg/kg doses compared with placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minimal effective dose: mean=0.26mg/kg or 8.4mg (range 0.1-0.5mg/kg or 2.5-20mg)</td>
</tr>
<tr>
<td>Gadow</td>
<td>1995</td>
<td>Fair</td>
<td>Placebo vs. 0.1mg/kg; Placebo vs. 0.3mg/kg; Placebo vs. 0.5mg/kg; 0.1mg/kg vs. 0.5mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Classroom observation--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. Interference: p&lt;0.05; p&lt;0.05; p&lt;0.01; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b. Motor: p&lt;0.05; p&lt;0.01; p&lt;0.01; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>c. Off-task: p&lt;0.01; p&lt;0.01; p&lt;0.01; p&lt;0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>d. Noncompliance: p&lt;0.01; p&lt;0.01; p&lt;0.01; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>e. Nonphysical aggression: NS; NS; NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lunchroom observation--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. Noncompliance: NS; p&lt;0.05; p&lt;0.01; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>b. Physical aggression: NS; NS; p&lt;0.01; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>c. Nonphysical aggression: NS; p&lt;0.01; &lt;0.05; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Playground observation:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. Nonphysical aggression: p&lt;0.01; p&lt;0.05; p&lt;0.05; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>School tic observations:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. Motor tic observation: p&lt;0.05; NS; NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minimal effective dose: mean=0.29mg/kg/bid or 8.8mg (range 2.5mg-20mg)</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadow</td>
<td>Stimulant Site Effects Checklist (SSEC) by parents</td>
<td>NS in SSEC</td>
<td>none</td>
<td>* no other side effect information</td>
</tr>
<tr>
<td>Gadow</td>
<td>NR</td>
<td>NR</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year (Quality)</td>
<td>Study Design</td>
<td>Setting</td>
<td>Eligibility criteria</td>
</tr>
<tr>
<td>--------</td>
<td>---------------</td>
<td>--------------</td>
<td>---------</td>
<td>----------------------</td>
</tr>
</tbody>
</table>
| Handen | 1990 Fair     | RCT DB crossover | 1. A score of 15 or more on the hyperactivity index of both the Conners Parent and Teacher Rating Scales.  
3. Intellectual functioning within the mild-to-borderline range of mental retardation (IQ score 50 to 74, mean=65, EMR in class placement) as measured either by the Wechsler Intelligence Scale for Children-Revised (Full-Scale IQ Score) or the Stanford-Binet: Fourth Edition (Composite Index)  
4. Adaptive functioning within the mild-to-borderline range of mental retardation as measured on the Vineland Adaptive Behavior Scale-Parent Version | 100% mental retardation and ADHD |
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen 1990</td>
<td>week 3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid (breakfast and lunch) for a 7-days period.</td>
<td>2 weeks</td>
<td>NR</td>
<td>Weekday classroom behavioral and attentional measures: Conners Teacher Rating Scale, CAP Behavior Checklist, Side Effects Checklist, Five-Minute Work Sample.</td>
<td>Mean age= NR, range 6-9 years.</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td>Saturday laboratory program attentional and behavioral measures: Eight-Minute Work Sample, Observation of Eight-Minute Work Sample, Observation of Group Instruction, Continuous Performance Test</td>
<td>Gender=11(91.7%) male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Saturday laboratory program learning measure: Paired Associate Learning Task</td>
<td>Race: NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Saturday laboratory program social behavior measures: global ratings</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>NR</td>
<td>NR/ NR/ 12 enrolled</td>
<td>0/0/0</td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Evidence Table 5. Placebo-controlled trials in children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>(Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1990</td>
<td>Fair</td>
<td>0.3mg/kg vs. placebo; 0.6mg vs placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weekday measures:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Teacher Conners--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. Conduct problems: p&lt;0.05; p&lt;0.05 b. Hyperactivity: p&lt;0.05; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>c. Inattention/ Passivity: p&lt;0.05; NS d. hyperactivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Index: p&lt;0.05; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Teacher CAP--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. Inattention: NS; p&lt;0.05 b. Overactivity: p&lt;0.05; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Independent Task--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. No. item completed: NS; NS b. % correct: NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Saturday measures:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Independent task--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. No. items completed: p&lt;0.05; NS b. % correct: NS; NS c. % on-task behavior: NS; p&lt;0.05 d. % in-seat behavior: NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>e. Global restlessness: NS; p&lt;0.05 f. Global interest: p&lt;0.05; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group instruction--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. % on-task behavior: NS; p&lt;0.05 b. % in-seat behavior: p&lt;0.05; p&lt;0.05 c. Global restlessness: p&lt;0.05; p&lt;0.05 d. Global</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>interest: NS; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Individual testing--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. CPT, % correct: NS; p&lt;0.05 b. CPT, no. impulsive: NS; p&lt;0.05 c. PALT, % correct: NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Social interaction/play--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. Solitary: NS; NS b. Interactivity: NS; NS c. Rough and tumble: NS; p&lt;0.05 d. Negative: NS; p&lt;0.05 e. Intense: NS; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Global measure/play--</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>a. Active: NS; NS b. Social: NS; p&lt;0.05 c. Aggressive: NS; NS</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>Reported by teachers</td>
<td>4(33.3%): drowsiness</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td>1(8.3%): drowsiness without staring</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1(8.3%): social withdrawal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
</table>
| Handen  | 1991 Fair     | RCT DB crossover |        | 1. Intellectual functioning within the mild to borderline range of mental retardation (IQ 48-74, mean=64), as measured either by the Wechsler Intelligence Scale for Children-Revised (Full-Scale IQ Score) or the Stanford-Binet Intelligence Scale: Fourth Edition (Composite Index), and educable mental retardation in class placement  
2. Adaptive functioning within the mild to borderline range of mental retardation, based upon the Vineland Adaptive Behavior Scale-Parent Version  
3. A score of 15 or more on Hyperactivity Index of both the Conners Abbreviated Teacher Rating Scale and the Conners Abbreviated Parent Rating Scale  
4. A diagnosis of ADHD based upon a semistructured interview with parents using DSM-III-R criteria | 100% mental retardation and ADHD |
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>week3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid (breakfast and lunch) for a 7-days period.</td>
<td>2 weeks</td>
<td>NR</td>
<td>Side Effect Checklist (6 point Likert Scale) by teachers: motor movement, drowsy, sad, staring, social withdrawal, irritability, poor appetite, anxiety, dizzy, moody, high activity, stomachache, headache</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean age=8.6, range 6.7-12.1 years  
Gender=22(81.5%) male  
Race: NR
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>NR</td>
<td>NR/NR/27 enrolled</td>
<td>13 withdrawn/o lost to fu/27 analyzed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Quality</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1991</td>
<td>Fair</td>
<td>18(67%) were identified as responders to methylphenidate.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo vs. 0.3mg/kg (N=27); Placebo vs. 0.6mg/kg (N=25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Irritability: NS; 14(51.8%): 3(12%), p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiety: NS; 11(40.7%): 3(12%), p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High activity: 21(77.8%): 9(33.3%), p&lt;0.05; 21(77.8%): 10(40%), p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Other side effects: NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo vs. 0.3mg/kg (N=14); Placebo vs. 0.6mg/kg (N=14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Staring: 2.0: 0.93, p&lt;0.05; 2.0: 0.75, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Irritability: 1.21:0.43, p&lt;0.05; 1.21: 0.33, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiety: 1.0: 0.86, NS; 1.0: 0.50, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moody: 0.79: 0.36, NS; 0.79: 0.00, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High activity: 3.0: 1.50, p&lt;0.05; 3.0: 0.75, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Other side effects: NS; NS</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1991</td>
<td>Side Effect Checklist (6 point Likert Scale) by teachers: motor movement, drowsy, sad, staring, social withdrawal, irritability, poor appetite, anxiety, dizzy, moody, high activity, stomachache, headache</td>
<td>18 (67%) were identified as responders to methylphenidate.</td>
<td>13 withdrawals due to adverse events</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td>Placebo vs. 0.3mg/kg (N=27); Placebo vs. 0.6mg/kg (N=25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Irritability: NS; 14 (51.8%): 3 (12%), p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiety: NS; 11 (40.7%): 3 (12%), p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High activity: 21 (77.8%): 9 (33.3%), p&lt;0.05; 21 (77.8%): 10 (40%), p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Other side effects: NS; NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo vs. 0.3mg/kg (N=14); Placebo vs. 0.6mg/kg (N=14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Staring: 2.0: 0.93, p&lt;0.05; 2.0: 0.75, p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Irritability: 1.21: 0.43, p&lt;0.05; 1.21: 0.33, p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiety: 1.0: 0.86, NS; 1.0: 0.50, p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moody: 0.79: 0.36, NS; 0.79: 0.00, p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High activity: 3.0: 1.50, p&lt;0.05; 3.0: 0.75, p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*Other side effects: NS; NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
</table>
| Handen | 1992 Fair      | RCT DB crossover |         | 1. A score of 15 or more on the hyperactivity index of both the Conners Parent and Teacher Rating Scales.  
3. Intellectual functioning within the mild-to-borderline range of mental retardation as measured either by the Wechsler Intelligence Scale for Children-Revised (Full-Scale IQ Score) or the Stanford-Binet: Fourth Edition (Composite Index)  
4. Adaptive functioning within the mild-to-borderline range of mental retardation as measured on the Vineland Adaptive Behavior Scale-Parent Version | 100% mental retardation and ADHD |
<p>| Fair   |                |              |         |                      |             |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>week 3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid (breakfast and lunch) for a 7-days period.</td>
<td>None</td>
<td>NR</td>
<td>Weekday classroom measures: Conners Teacher Scale, Child Attention Problems (CAP), Five-minute work sample</td>
<td>Mean age=9.1, range 6-12 years</td>
<td>Gender=10(71.4%) male</td>
<td>Race: 6(42.9%) Africa American</td>
</tr>
<tr>
<td>1992</td>
<td>Fair</td>
<td></td>
<td></td>
<td>Saturday laboratory program attentional and behavioral measures: Ten-minute work sample, Observation of 10 minute work sample (academic task), Observation of group instruction (academic task), observation of arts and crafts session (nonacademic task), Continuous Performance Test (CPT), Paired Associate Learning Task (PAL), Selective Reminding Task (SRT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Saturday laboratory program social behavior measures: Playgroup observation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Evidence Table 5. Placebo-controlled trials in children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1992 Fair</td>
<td>Hollingshead socioeconomic status: middle- to upper-class: 7(50%) working class: 7(50%)</td>
<td>NR/ NR/ 14 enrolled</td>
<td>0/0/14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IQ score 48 to 74, mean=65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1992 Fair</td>
<td>Placebo vs. 0.3mg/kg; Placebo vs. 0.6mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weekday measures:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conners Teacher Rating Scale--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. Conduct problems: NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Hyperactivity: NS; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. Inattention/passivity: p&lt;0.05; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>d. Hyperactivity Index: NS; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teacher CAP Rating Scale--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. Inattention: NS; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Overactivity: NS; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. total: NS; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Independent task: NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Saturday measures:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conners Teacher Rating Scale--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. Conduct problems: NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Hyperactivity: p&lt;0.05; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. Inattention/passivity: p&lt;0.05; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>d. Hyperactivity Index: p&lt;0.05; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teacher CAP Rating Scale--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. Inattention: p&lt;0.05; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Overactivity: p&lt;0.05; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. total: p&lt;0.05; p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Independent task: NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Individual testing:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. CPT correct and impulsive %: NS; NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. PAL and SRT correct %: NS; NS</td>
</tr>
</tbody>
</table>
**Evidence Table 5. Placebo-controlled trials in children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>NR</td>
<td>NR</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

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

Source: Final Report Drug Effectiveness Review Project
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1994 Fair</td>
<td>2 doses of methylphenidate; (0.3 and 0.6mg/kg per dose) and a placebo.</td>
<td>NR</td>
<td>NR</td>
<td>Connors Parent Rating Scale, Connors Teacher Rating Scale, Continuous Performance Test,</td>
<td>n= 47</td>
<td>6.1 -12.5 years of age</td>
<td>31 males/ 33 Caucasians</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1994 Fair</td>
<td>Families distributed across socioeconomic levels, using Hollingshead Four-Factor Index: 4.3% Level 1, 19.1% Level 2, 27.7% Level 3, 10.6% Level 4</td>
<td>NR/NR/47 enrolled</td>
<td>NR/NR/47</td>
</tr>
</tbody>
</table>
**Evidence Table 5. Placebo-controlled trials in children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1994 Fair</td>
<td><strong>Stepwise Multiple Regression Analyses using Parent and Demographic Information to Predict School Drug Response</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Outcome Variable; predictor Variable; b Coefficient; pValue ; r2</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Connors Scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity; Sex; -5.23; .0438; .0955</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inattention; impulsivity-hyperactivity (P); .94; .0084; .1574</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conduct Problems; Sex; -5.32; .0139; .1041</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of problems completed;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conduct Problems (P); 1.39; .0025; 0.1127</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IQ; -1.04; .0075; .0026; .2629</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% of problems correct</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mental Age; .03; .0074; .1456</td>
</tr>
<tr>
<td></td>
<td></td>
<td>On-task (independent); -.20; .0095; .0015; .2827</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Stepwise Multiple Regression Analyses Using Parent and Demographic Information to Predict Saturday Laboratory Drug Response</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>On-task (independent); Hyperactivity index (T); -26.64; .0009; .2210</td>
</tr>
<tr>
<td></td>
<td></td>
<td>On-task (group); no variables</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Connors Scale</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperactivity index; Hyperactivity Index (T); 0.83; .0021; .1912</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inattention; Hyperactivity Index (T); 0.47; .0030; .0927</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Race; -.37; .0060; .2377</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conduct Problems; Hyperactivity (T); .72; .0006; .2335</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPT % Correct; SES (Level 2); 152.97; .0481; .0841</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPT No. of Responses; Impulsivity-Hyperactivity Index (P); 5.01; .0036; .1149</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conduct Problems (T); 2.55; .0001; .2259</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Race; -21.57; .0076; .3764</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conduct Problems (P); -1.08; .0239; .4486</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen 1994</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NR** indicates not reported.
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1995</td>
<td>RCT DB crossover</td>
<td>Children with mental retardation and ADHD served as subjects. All subjects met the following inclusion criteria: (1) a score of 15 or more on the Hyperactivity Index of both the Conners Parent and Teacher Rating Scales while off medication, and (2) intellectual functioning within the moderate to borderline range of mental retardation as measured by the Weschler Intelligence Scale for Children-Revised or the Stanford-Binet Intelligence Scale(Composite Index).</td>
<td>100% mental retardation and ADHD</td>
</tr>
<tr>
<td>Author</td>
<td>Interventions and total daily dose</td>
<td>Run-in/Washout Period</td>
<td>Allowed other medications/interventions</td>
<td>Method of Outcome Assessment and Timing of Assessment</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>-----------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Handen 1995</td>
<td>week3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid with breakfast and lunch for a 7-days period.</td>
<td>2 weeks</td>
<td>NR</td>
<td>Independent Play: each Saturday morning after medication. Restricted Academic Task: each Saturday afternoon after medication.</td>
</tr>
</tbody>
</table>
|             |                                                                                                  |                       |                                          |                                                                                                                       | Race: 17(77%)
Caucasian, 4(18%)
Black, 1(5%)
Hispanic                                                                 |
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1995</td>
<td>Mean IQ =64(8.8), range 50-77 Hollingshead four-factor Index for social-economic status (Level): I -- 1(5%) II -- 5(23%) III -- 8(36%) IV -- 2(9%) V -- 6(27%)</td>
<td>NR/NR/22 enrolled</td>
<td>none/none</td>
</tr>
</tbody>
</table>

Pharmacologic Treatments for ADHD Page 358 of 616
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Results</th>
</tr>
</thead>
</table>
| Handen  | 1995 | **Independent Play:**  
|         |      | Intense -- 0.3mg/kg=0.6mg/kg>placebo (p=0.005) |
|         |      | Vocalization -- 0.3mg/kg=0.6mg/kg>placebo (p=0.001) |
|         |      | Movement -- 0.6mg/kg>placebo (p=0.009) |
|         |      | Noninvolved -- no difference |
|         |      | Nontoy item -- no difference |
|         |      | Toy pickup -- 0.6mg/kg>0.3mg/kg (p=0.006) |
|         |      | Toy leaves -- 0.6mg/kg>0.3mg/kg (p=0.008) |
|         |      | Length of time playing with toys (1-20s) -- no difference |
|         |      | Length of time playing with toys (20-120s) -- 0.6mg/kg>0.3mg/kg (p=0.004) |
|         |      | Length of time playing with toys (>120s) -- no difference |
|         |      | **Restricted Academic Task:**  
<p>|         |      | On-task -- 0.3mg/kg=0.6mg/kg&gt;placebo (p=0.001) |
|         |      | Distracted -- no difference |
|         |      | Touch toy -- 0.3mg/kg=0.6mg/kg&gt;placebo (p=0.001) |
|         |      | Fidget -- no difference |
|         |      | Out of seat -- 0.6mg/kg&gt;placebo, 0.6mg/kg&gt;0.3mg/kg (p=0.001) |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen 1995</td>
<td>NR</td>
<td>2(9%) had significant adverse medication side effects experience, so the 0.6mg/kg MPH dose was not given at 11:45am during the Saturday Laboratory program.</td>
<td>None. Missing data were imputed using a maximum likelihood technique</td>
<td>none</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1996</td>
<td>RCT DB crossover</td>
<td>All subjects met the following criteria: (1) a score of 15 or more on the Hyperactivity Index of both the Conners Parent and Teacher Rating Scales while off medication, and (2) intellectual functioning within the moderate range of mental retardation to borderline intellectual functioning, as measured by the Weschler-Intelligence Scale for children-revised or the Stanford-Binet Intelligence Scale-Fourth Edition (Composite Index).</td>
<td>100% mental retardation and ADHD</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen 1996</td>
<td>week 3-5: 0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid with breakfast and 3.5-4 hours later with lunch for a 7-days period.</td>
<td>2 weeks</td>
<td>NR</td>
<td>Behavior problem checklists: teachers completed the Conners Hyperactivity Index, the Conners Inattentiveness/Passivity Scale and the CAP Inattention scale at the end of each drug condition.</td>
<td>Age (months): mean=103.93, range 73-160</td>
<td>Gender: 23(52.3%)</td>
<td>Race: 32(72.7%) Caucasian, 12(27.3%) other</td>
</tr>
</tbody>
</table>

Saturday laboratory measures: the Selective Remaining Task (SRT) was given during each drug condition. Weekday classroom measures: a daily 5-min work task similar to the one in the Saturday classroom was given, and the average number of problems completed and percentage correct was calculated.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1996</td>
<td>Mean IQ =64.25(9.06), range 44-77 Hollingshead four-factor Index for social-economic status (Level): I -- 1(2.3%) II -- 12(27.3%) III -- 14(31.8%) IV -- 6(13.6%) V -- 11(25%)</td>
<td>NR/NR/44 enrolled</td>
<td>0/0/0</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1996</td>
<td>29(66%) responded to MPH (based on a 50% or greater decrease in Teacher Conners Hyperactivity Index)</td>
</tr>
</tbody>
</table>

Weekday classroom measures:
- Conners Hyper. Index: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001
- Conners Inatten./Pass.: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001
- CAP Inattention: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001
- No. Problems completed: 0.6mg/kg> placebo, p<0.05
- Percentage correct: 0.3mg/kg> placebo, p<0.05

Saturday classroom measures:
- Conners Hyper. Index: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001
- Conners Inatten./Pass.: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001
- CAP Inattention: 0.3mg/kg, 0.6mg/kg>placebo, p<0.001
- No. Problems completed: 0.6mg/kg> placebo, p<0.001
- Percentage correct: no sig. diff.

SRT: NS
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>NR</td>
<td>3(6.8%) had significant side effects experience (e.g., motor tics, lip smacking, headaches, dizziness, high blood pressure), so the medication was not given during one of the drug condition.</td>
<td>none. Missing data (4%) were imputed using mean replacement</td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1997</td>
<td>RCT DB</td>
<td>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.</td>
<td>mental retardation and ADHD</td>
</tr>
<tr>
<td></td>
<td>Fair</td>
<td>RCT DB crossover</td>
<td>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.</td>
<td>9(82%) ADHD, 2(18%) oppositional defiant disorder.</td>
</tr>
</tbody>
</table>
# Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen 1997</td>
<td>methylphenidate (MPH) *no dosage, duration and schedule information</td>
<td>NR</td>
<td>NR</td>
<td>Baseline Home Measures: Conner Parent Rating Scale</td>
<td>Age (months): mean=130.4, range 86-178</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>1 week before intervention</td>
<td>NR</td>
<td></td>
<td>Baseline Weekday Classroom Measures: Conners Teacher Rating Scale and Classroom Assignment</td>
<td>Gender: 32(62.7%) male</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1-5 years Follow-up Measures: age, length of follow-up, classroom assignment, medication history, nonpharmacologic interventions, inpatient treatment, school suspensions, police involvement, conners parent rating scale.</td>
<td></td>
<td></td>
<td></td>
<td>Race: 37(72.5%) Caucasian, 13(25.5%) Black, 1(2%) Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handen 1999</td>
<td>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.</td>
<td>1 week before intervention</td>
<td></td>
<td>Preschool Classroom Measures at the last day of each phase (weekly): Conners Teacher Rating Scale, Preschool Behavior Questionnaire, Side Effects Checklist</td>
<td>Age: mean=4.9, range 4-5.11 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td>Laboratory Measures (weekly): Waiting Task, Resistance to Temptation, Play Session, Compliance Task, Clean-up Task.</td>
<td>Gender: 9(82%) male</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Race: NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Age (months):** mean=130.4, range 86-178
Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/ eligible/ enrolled</th>
<th>Number withdrawn/ lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1997 Fair</td>
<td>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%)</td>
<td>NR/NR/51 enrolled</td>
<td>0/0/0</td>
</tr>
</tbody>
</table>

Handen 1999 Mean IQ=60(11.6), range 40-78 NR/NR/11 enrolled 1 withdraw/ 0 lost/ 10 analyzed
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
</table>
| Handen | 1997 Fair     | Initial vs. follow-up:  
Conduct problem (CA), p=0.041  
Conduct problem (MA), p=0.097 |
| Fair   |               | Anxiety (CA), p=0.295  
Anxiety (MA), p=0.041  
Impulsivity-Hyperactivity (CA), p=0.003  
Impulsivity-Hyperactivity (MA), p=0.007  
Learning problem (CA), p<0.005  
Learning problem (MA), p<0.005  
Psychosomatic (CA), p=0.947  
Psychosomatic (MA), p=0.569  
Hyper. Index (CA), p<0.005  
Hyper. Index (MA), p<0.005 |
| Handen | 1999 Fair     | 8(73%) responded to the drugs (based on a 40% or more decrease in Teacher-rated Conners Hyperactivity Index and/or Hyperactive-Distractible subscale) |
| Fair   |               | Dull, social withdrawal, poor appetite, anxiety, and drowsiness were reported more in the drugs than placebo (mean):  
Dull -- placebo(0.4), 0.3mg/kg(1.5), 0.6mg/kg(2.2)  
Social withdrawal -- placebo(0.4), 0.3mg/kg(1.3), 0.6mg/kg(2.1)  
Poor appetite -- placebo(0.1), 0.3mg/kg(1.9), 0.6mg/kg(3.2)  
Anxiety -- placebo(0), 0.3mg/kg(0.1), 0.6mg/kg(0.3)  
Drowsiness -- placebo(0), 0.3mg/kg(1.1), 0.6mg/kg(0.6) |
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>1997 Fair</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parents or teachers reported</td>
<td>5(4.5%) patients were reported with severe adverse side effects with 0.6mg/kg dose.</td>
<td>1 (9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dull, social withdrawal, poor appetite, anxiety, and drowsiness were reported more in the drugs than placebo (mean):</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dull -- placebo(0.4), 0.3mg/kg(1.5), 0.6mg/kg(2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Social withdrawal -- placebo(0.4), 0.3mg/kg(1.3), 0.6mg/kg(2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor appetite -- placebo(0.1), 0.3mg/kg(1.9), 0.6mg/kg(3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiety -- placebo(0), 0.3mg/kg(0.1), 0.6mg/kg(0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drowsiness -- placebo(0), 0.3mg/kg(1.1), 0.6mg/kg(0.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Study Design</td>
<td>Setting</td>
<td>Eligibility criteria</td>
<td>Comorbidity</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>--------------------</td>
<td>-----------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Handen</td>
<td>RCT DB crossover</td>
<td>Children with autism/PDD serviced as subjects. The inclusion criteria were employed: (a) a score of 30 or more on a parent-completed Child Autism Rating Scale (CARS), (b) a diagnosis of Autism or Pervasive Developmental Disorder Not Otherwise Specified (PDDNOS) made by a board-certified child psychiatrist, and (c) a score of 15 points or more on the Hyperactivity Index of the Teacher Conners Rating Scale while off all psychotropic medication.</td>
<td>9(69%) Autistic disorder, 4(31%) Pervasive Development Disorder Not Otherwise Specified (PDDNOS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agarwal</td>
<td>RCT DB, crossover.</td>
<td>Children 6-15 years with hyperkinetic disorder</td>
<td>100% had mental retardation, 2 (20%) had seizure disorder, 1 (10%) had congenital hypothyroidism, 5 (50%) had conduct disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Setting: 1 clinic in a university setting in India.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen 2000</td>
<td>0.3mg/kg methylphenidate (MPH), 0.6mg/kg MPH, or placebo: bid with breakfast and 4 hours later with lunch for a 7-days period.</td>
<td>NR</td>
<td>NR</td>
<td>Weekly after each MPH condition by teachers or program staffs: Conners Teacher Scale, IOWA Conners Teacher Rating Scale, Aberrant Behavior Checklist, Child Autism Rating Scale(CARS), Side Effect Checklist</td>
<td>Age: mean=7.4, range 5.6-11.2 years</td>
<td>Male</td>
<td>Race: 4(31%) Caucasian, 7(54%) African American, 2(15%) Hispanic</td>
</tr>
<tr>
<td>Agarwal 2001</td>
<td>Clonidine 4-, 6-, and 8-mcg/kg/day in two or three divided doses for 2 weeks each for a total period of 6 weeks than placebo for following 6 weeks. Crossover group was reversed, placebo first than clonidine.</td>
<td>None/one month without medication for hyperkinetic disorder</td>
<td>NR</td>
<td>The Hillside Behavior Rating Scale (HBRS); Parent symptom questionnaire (PSQ) and clinical global impression scale (CGI)</td>
<td>Age: 6-15 years (mean NR)</td>
<td>Male: 8 (80%)</td>
<td>Ethnicity: Study conducted in India, presume all children of Indian decent</td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>2000 Fair</td>
<td>Mental retardation level:</td>
<td>NR/NR/13 enrolled</td>
<td>0 withdrawn / 1 lost / 12 analyzed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe/profound=3(23%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate=5(38%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild/Borderline=4(31%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Average IQ=1(8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agarwal</td>
<td>2001 Fair</td>
<td>NR</td>
<td>11/11/10</td>
<td>0/0/10</td>
</tr>
</tbody>
</table>

Pharmacologic Treatments for ADHD
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>(Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>2000</td>
<td>Fair</td>
<td>8 (61.5%) were determined to be MPH responders (based on a minimum 50% decrease on the Teacher Conners Hyperactivity)</td>
</tr>
<tr>
<td>Agarwal</td>
<td>2001</td>
<td>Fair</td>
<td>Conners: 0.3mg/kg&gt;placebo, p&lt;0.005; 0.6mg/kg&gt;placebo, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IOWA: 0.3mg/kg&gt;placebo, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aberrant Behavior Checklist:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Irritability--NS; Lethargy--NS; Stereotypy--NS;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity--0.6mg/kg&gt;placebo, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>inappropriate speech--NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CARS: NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Clonidine 4mcg/kg/day vs Clonidine 6mcg/kg/day vs Clonidine 8mcg/kg/day vs Placebo</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PSQ factor and total mean score differences after treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conduct: 0.9 (6.8-5.9) vs 1.5 (6.8-5.3) vs 2.7 (6.8-4.1) vs 0.01 (6.8-6.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impulsive hyperactive: 1.8 (15.6-13.8) vs 4.7 (15.6-10.9) vs 7.7 (15.6-7.9) vs 0.03 (15.6-15.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total: 10.2 (78.7-68.5) vs 17 (78.7-61.7) vs 26.9 (78.7-51.8) vs 2.2 (78.7-76.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HBRS mean score differences after treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gross-motor: 1.2 (5.1-3.9) vs 2.0 (5.1-3.1) vs 2.7 (5.1-2.4) vs 0.3 (5.1-4.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Distractibility and concentration: 0.8 (3.5-2.7) vs 1.3 (3.5-2.2) vs 1.4 (3.5-2.1) vs 0.1 (3.5-3.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Frustration tolerance: 0.2 (2.6-2.4) vs 0.6 (2.6-2.0) vs 0.8 (2.6-1.8) vs 0 (2.6-2.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cooperation: 0.6 (3.5-2.9) vs 1.1 (3.5-2.4) vs 1.1 (3.5-2.4) vs 0.1 (3.5-3.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interest in task: 0.4 (3.5-3.1) vs 0.7 (3.5-2.8) vs 1.0 (3.5-2.5) vs 0.2 (3.5-3.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impulsivity: 0.5 (3.5-3.0) vs 0.8 (3.5-2.7) vs 1.4 (3.5-2.1) vs 0 (3.5-3.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CGI mean severity differences after treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.4 (4.6-4.2) vs 1.1 (4.6-3.5) vs 1.9 (4.6-2.7) vs 0.1 (4.6-4.5)</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen</td>
<td>2000 Fair</td>
<td>Parents or teachers reported</td>
<td>Side Effect Checklist rated by teachers</td>
<td>2 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Agarwal</td>
<td>2001 Fair</td>
<td>NR</td>
<td>Drowsiness (50%), drymouth (10%), anorexia (10%), drop in systolic blood pressure (decreased by 3%-8.9%) (70%)</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein</td>
<td>1988 Poor</td>
<td>Randomized experimental study; unblinded</td>
<td>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</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
| Zeiner      | 1999 Fair      | RCT, DB, crossover          | 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 | 4(19%) had developmental reading disorder  
5(24%) showed delayed development of motor functions  
13(62%) was diagnosed as oppositional defiant disorder |
<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein</td>
<td>Condition (A)=&quot;ON&quot;, remain &quot;ON&quot; a methylphenidate regimen all throughout up to 3-years, including summers</td>
<td>NR/NR</td>
<td>NR</td>
<td>NR</td>
<td>Mean age=9 years</td>
</tr>
<tr>
<td>Poor</td>
<td>Condition (B)=&quot;OFF&quot;, go &quot;OFF&quot; methylphenidate during each of two consecutive summers, with reinstatement between summers for up to 3 years</td>
<td></td>
<td></td>
<td></td>
<td>91% male</td>
</tr>
<tr>
<td></td>
<td>Dosage ranges/mean dosages NR</td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity NR</td>
</tr>
<tr>
<td>Zeiner</td>
<td>Methylphenidate mean dose=22.4mg/day, range 15mg-35mg duration: 3 weeks</td>
<td>NR/1 week</td>
<td>NR</td>
<td>Parental Account of Childhood Symptoms (PACS) Conners's Teacher Rating Scale (CTRS) Children's Checking Task (CCT) Continuous Performance Test (CPT) Paced Auditory Serial-Addition Task (PASAT) Maze Coordination Test (MCT) Grooved Pegboard Test (GPT) Reliable Change Index (RCI)</td>
<td>Mean age=8.8 years</td>
</tr>
<tr>
<td>Fair</td>
<td>dosage schedule: NR</td>
<td></td>
<td></td>
<td></td>
<td>100% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity NR</td>
</tr>
<tr>
<td>Author</td>
<td>Year &lt;br&gt;(Quality)</td>
<td>Other population characteristics (mean scores)</td>
<td>Number screened/eligible/enrolled</td>
<td>Number withdrawn/lost to fu/analyzed</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Klein</td>
<td>1988 &lt;br&gt;Poor</td>
<td>Height=133.4 cm &lt;br&gt;Weight=27.9 kg</td>
<td>NR/NR/62</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Zeiner</td>
<td>1999 &lt;br&gt;Fair</td>
<td>NR</td>
<td>NR/NR/21</td>
<td>NR/NR/21</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein</td>
<td>1988 Poor</td>
<td>NR</td>
</tr>
</tbody>
</table>
| 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  
Fair  
CCT commission errors- 1.1: 1.0, NS; CCT omission errors- 2.7: 4.6, p<0.05  
CPT commission errors- 4.6: 7.6, NS; CPT omission errors- 7.8: 13.8, p<0.05  
PASAT R version- 8.8: 8.4, NS; PASAT S version- 8.2: 7.4, NS  
MCT dominant hand- 3.9: 12.0, p<0.05; MCT non-dominant hand- 30.8: 35.5, NS  
GPT dominant hand- 67.7: 74.9, p<0.05; GPT non-dominant hand- 83.7: 91.6, NS  
RCI showed significant improvement in methylphenidate treatment |
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein</td>
<td>1988 Poor</td>
<td>Height and weight were obtained routinely by secretaries in all clinic children before and after the summer with a medical scale</td>
<td>ON vs OFF, t-score, p-value</td>
<td>NR</td>
<td>Retrospective analysis of height/weight data from a study designed to measure efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Weight (kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>One summer: 134.3 vs 134.4, t=0.73, p=NS</td>
<td>One summer: 28.6 vs 29.5, t=2.98, p=0.005</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Two summers: 138.3 vs 139.8, t=2.57, p=0.02</td>
<td>Two summers: 32.2 vs 32.8, t=0.88, p=NS</td>
<td></td>
</tr>
<tr>
<td>Zeiner</td>
<td>1999 Fair</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Final Report Drug Effectiveness Review Project
**Evidence Table 5. Placebo-controlled trials in children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleator</td>
<td>1974 Poor</td>
<td>Long-term continuous follow-up</td>
<td>Children who had previously been in a DB, placebo-controlled study. These children scored $\geq 15$ (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).</td>
<td>NR</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/ interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age Gender Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleator</td>
<td>1974 Poor</td>
<td>Mean daily dose: 0.66 mg/kg or 20.5 mg (41 subjects took doses once a day, in the morning)</td>
<td>Not applicable</td>
<td>NR</td>
<td>ASQ ratings were obtained from each subject's teacher at the end of each school month. Report cards and written reports from teachers were also obtained.</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleator 1974</td>
<td>NR</td>
<td>NR/NR/42</td>
<td>NR/NR/28</td>
</tr>
</tbody>
</table>

Poor
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Quality</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleator</td>
<td>1974</td>
<td>Poor</td>
<td>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 &quot;increased-dose&quot; subgroup. The remaining 10/17 are called the &quot;drug-benefited&quot; group. 11/42 scored adequate functioning (ASQ score &lt;15) during the placebo month (the &quot;remission&quot; 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 &quot;remission&quot; group (no data given).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean ASQ Rating (placebo, 0.1 mg/kg, 0.3 mg/kg, and 0.7 mg/kg): 17, 15.8, 15.0, 11.8 (estimated from graph). Mean ASQ Score (pre-placebo, placebo, postplacebo - estimated from graph):</td>
</tr>
</tbody>
</table>
|        |      |        | Drug-Benefited Group: 8, 17.5, 8.5  
Increased Dose Group: 17, 23.8, 14  
Remission Group: 7.8, 7.0, 7.7  |
|        |      |        | Mean ASQ for all subjects when receiving medication (placebo eliminated) for Sep, Oct, Nov, Dec, Jan, Feb, Mar, Apr, May: 10, 9.5, 11, 12, 11, 12.5, 11.3, 11.3, 10.8 (estimated from graph)  |
**Evidence Table 5. Placebo-controlled trials in children**

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleator 1974</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Refer to Sprague 1973 for more details on study population? Also, FU group listed as 42, but really they only published data on 28</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold</td>
<td>2004 Poor</td>
<td>RCT placebo controlled withdrawal</td>
<td>Setting: 7-center US</td>
<td>Children and adolescents with ADHD based on DSM-III-R</td>
<td>d-MPH: placebo ADHD type Inattentive- 7(20%): 8(20%) combined- 28(80%): 32(80%) Stimulant naïve- 29(82.9%): 25(62.5%)</td>
</tr>
</tbody>
</table>
# Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Interventions and total daily dose</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold 2004</td>
<td>Dexamethylphenidate 5-20mg/day</td>
<td>NA</td>
<td>NR</td>
<td>Swanson, Nolan and Pelham- ADHD scale (SNAP-ADHD) rated by parents</td>
<td>MPH group: n=35</td>
<td>Mean age=10.1 years</td>
<td>Gender: 85.7% male</td>
</tr>
<tr>
<td>Placebo group: n=40</td>
<td>Mean age=9.9 years</td>
<td>Gender: 77.5% male</td>
<td>Ethnicity: 75%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration: 6 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year (Quality)</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold</td>
<td>2004 Poor</td>
<td>d-MPH: placebo</td>
<td>116/89/89</td>
<td>5/3/75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Teacher SNAP-ADHD- 0.7: 0.7</td>
<td></td>
<td>6 with other reasons</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parent SNAP-ADHD- 0.65: 0.55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Quality</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold</td>
<td>2004</td>
<td>Poor</td>
<td>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 )).</td>
</tr>
</tbody>
</table>
## Evidence Table 5. Placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold</td>
<td>2004</td>
<td>reported by patients</td>
<td>46% of d-MPH patients and 38% of placebo patients experienced at least one AE, which is generally mild.</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Comments: NR

Total withdrawals; withdrawals due to adverse events.
### Evidence Table 6. Quality of placebo-controlled trials in children

#### Internal Validity

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No</td>
</tr>
<tr>
<td>Kelsey 2004</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No</td>
</tr>
<tr>
<td>Spencer 2002</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>NR</td>
</tr>
<tr>
<td>Michelson 2002</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No</td>
</tr>
<tr>
<td>Michelson 2001</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No</td>
</tr>
<tr>
<td>Biederman 2002</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No</td>
</tr>
<tr>
<td>Michelson 2004</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No</td>
</tr>
</tbody>
</table>
### Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serious medical illness, a history of psychosis or bipolar disorder, alcohol or drug abuse within the past 3 months, and ongoing use of psychoactive medications other than the study drug</td>
<td>5-day washout</td>
</tr>
<tr>
<td>Kelsey 2004</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
<td>260/197/197</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spencer 2002</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
<td>409/291/291</td>
<td>Poor metabolizers of CYP2D6; weight &lt; 25 kg; documented history of bipolar I or II disorder or any history of psychosis; organic brain disease or a history of any seizure disorder, were taking any psychotropics; had any history of alcohol or drug abuse within the past 3 months; significant prior or current medical conditions</td>
<td>2-week washout</td>
</tr>
<tr>
<td>Michelson 2002</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR171</td>
<td>Serious medical illness, a history of psychosis or bipolar disorder, alcohol or drug abuse within the past 3 months, and ongoing use of psychoactive medications other than the study drug</td>
<td>5-day washout</td>
</tr>
<tr>
<td>Michelson 2001</td>
<td>Yes</td>
<td>No</td>
<td>Good</td>
<td>381/297/297</td>
<td>IQ&lt;80 as assessed by the WISC-III; serious medical illness, comorbid psychosis or bipolar disorder, history of a seizure disorder, or ongoing use of psychoactive medications other than the study drug</td>
<td>12-18 day washout</td>
</tr>
<tr>
<td>Biederman 2002</td>
<td>Yes</td>
<td>No</td>
<td>Good</td>
<td>NR/NR/604</td>
<td>Bipolar disorder; psychotic illness; unstable medical illness or patients with a condition that would require ongoing administration of a psychoactive medication</td>
<td>Washout of at least 5 times the plasma half-life</td>
</tr>
<tr>
<td>Michelson 2004</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/604</td>
<td>Bipolar disorder; psychotic illness; unstable medical illness or patients with a condition that would require ongoing administration of a psychoactive medication</td>
<td></td>
</tr>
</tbody>
</table>
# Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomoxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelsey 2004</td>
<td>No</td>
<td>Yes</td>
<td>Lilly</td>
<td>Yes</td>
</tr>
<tr>
<td>Spencer 2002</td>
<td>No</td>
<td>Yes</td>
<td>Lilly</td>
<td>Yes</td>
</tr>
<tr>
<td>Michelson 2002</td>
<td>No</td>
<td>Yes</td>
<td>Lilly</td>
<td>Yes</td>
</tr>
<tr>
<td>Michelson 2001</td>
<td>No</td>
<td>Yes</td>
<td>Lilly</td>
<td>Yes</td>
</tr>
<tr>
<td>Biederman 2002</td>
<td>No</td>
<td>Yes</td>
<td>Lilly</td>
<td>Yes</td>
</tr>
<tr>
<td>Michelson 2004</td>
<td>No</td>
<td>Yes</td>
<td>Lilly</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 6. Quality of placebo-controlled trials in children

*Internal Validity*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casat 1987</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR, NR, NR, NR</td>
<td>No</td>
</tr>
<tr>
<td>Connors 1996</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR, NR, NR, NR</td>
<td>Unclear</td>
</tr>
<tr>
<td><strong>Daviss</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001 United States</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, Yes, NR</td>
<td>No</td>
</tr>
<tr>
<td><strong>Clonidine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singer 1995</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hunt 1985</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR, NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Scahill 2001</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>
### Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>United States</td>
<td>Unclear</td>
<td>No</td>
<td>Poor</td>
<td>NR/NR/31</td>
<td>IQ &lt; 70 on WISC-R; history of seizure disorder, tic disorder, any unstable medical conditiona, and known hypersensitivity to psychotropic medications</td>
<td>14-day washout</td>
</tr>
<tr>
<td>Casat 1987</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Connors 1996</td>
<td>United States</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/109</td>
<td>WISC-R IQ &lt; 70; body weight &lt; 20 kg; girls who had passed menarche; known hypersensitivity to psychotropic medications; history or presence of seizure or tic disorders</td>
<td>14-day washout</td>
</tr>
<tr>
<td>Daviss 2001</td>
<td></td>
<td>Unclear</td>
<td>No</td>
<td>Poor</td>
<td>NR/29/25</td>
<td>Pervasive developmental disorders, mental retardation, bipolar disorders, psychosis, bulimia or anorexia nervosa, current alcohol or drug abuse/dependence, Tourette's disorder, and history of a seizure disorder; serious medical problems, weight M 25 kg; known hypersensitivity to bupropion; females sexually active without contraception</td>
<td>2-week single blind placebo lead-in</td>
</tr>
<tr>
<td>Poor Quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>United States</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>58/37/37</td>
<td>NR</td>
<td>Evidence of current major depression, generalized anxiety disorder, separation anxiety disorder, or psychotic symptoms; WISC-R IQ &lt; 70; prior adequate trial of guanfacine (dose of &gt;/= 1.5 mg/day for at least 2 weeks)</td>
</tr>
<tr>
<td>Singer 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hunt 1985</td>
<td></td>
<td>No</td>
<td>No</td>
<td>Poor</td>
<td>NR/NR/12</td>
<td>NR</td>
<td>Evidence of current major depression, generalized anxiety disorder, separation anxiety disorder, or psychotic symptoms; WISC-R IQ &lt; 70; prior adequate trial of guanfacine (dose of &gt;/= 1.5 mg/day for at least 2 weeks)</td>
</tr>
<tr>
<td>Scahill 2001</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>50/40/34</td>
<td>Evidence of current major depression, generalized anxiety disorder, separation anxiety disorder, or psychotic symptoms; WISC-R IQ &lt; 70; prior adequate trial of guanfacine (dose of &gt;/= 1.5 mg/day for at least 2 weeks)</td>
<td>Placebo washout of 7-14 days</td>
</tr>
</tbody>
</table>
### Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Casat 1987</td>
<td>No</td>
<td>Yes</td>
<td>Burroughs-Wellcome Company</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Connors 1996</strong></td>
<td></td>
<td>Yes</td>
<td>NIMH grant; 2 authors are Glaxo-Wellcome scientists</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Daviss 2001 United States</strong></td>
<td>No</td>
<td>Yes</td>
<td>Glaxo-Wellcome</td>
<td>Yes</td>
</tr>
<tr>
<td>Poor Quality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clonidine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singer 1995</td>
<td>No</td>
<td>Yes</td>
<td>Tourette Syndrome Association and US</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Hunt 1985</strong></td>
<td></td>
<td>Yes</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td><strong>Scahill 2001</strong></td>
<td>100% guanfacine naïve</td>
<td>Yes</td>
<td>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</td>
<td>Yes</td>
</tr>
</tbody>
</table>
**Evidence Table 6. Quality of placebo-controlled trials in children**

*Internal Validity*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenhill 2002</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No</td>
</tr>
<tr>
<td>Rugino 2003</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>None</td>
</tr>
</tbody>
</table>
## Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenhill 2002</td>
<td>Rugino 2003</td>
<td>No, 2 patients excluded</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/24</td>
<td>(1) acute medical or uncontrolled psychiatric illness; (2) allergy to modafinil or any of the components of the tablet; (3) mitral valve prolapse, left ventricular hypertrophy, cardiac ischemia, clinically significant cardiac arrhythmia, or history of syncope; (4) use of the following medications within 30 days before the study: psychoactive medications other than stimulants prescribed to manage ADHD, antiepileptics, or medications metabolized primarily through the hepatic cytochrome P450 system; (5) more than 3 migraine headaches within 3 months before the study; (6) female with potential of becoming pregnant during the study; (7) uncontrolled seizure disorder; (8) sleep disorder with insomnia; and (9) history of manic episodes or psychosis</td>
<td>1-week SB placebo washout - excluded any that responded to placebo during these phase</td>
</tr>
</tbody>
</table>

Exclusion criteria: comorbid psychiatric diagnosis; history of seizure, tic disorder, or family history of Tourette's syndrome; female having undergone menarche; use of amphetamines, pemoline, or an investigational drug within 30 days of study entry; concomitant use of clonidine, anticonvulsant drugs, or medications known to affect blood pressure, heart rate, or central nervous system function; hyperthyroidism or glaucoma; any concurrent chronic or acute illness (eg, allergic rhinitis, severe cold) or disability that could confound the study results. Also excluded were children who had failed a previous trial of stimulants for ADHD, had required a third daily dose in the afternoon or evening, had a documented allergy or intolerance to MPH, or were living with anyone who currently had substance abuse disorder (excluding dependency).
<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenhill 2002</td>
<td>No</td>
<td>Yes</td>
<td>Celltech Pharmaceuticals, Inc.</td>
<td>Low relevance because of bias towards Metadate® arm by excluding 45 children who &quot;responded&quot; to placebo during washout phase.</td>
</tr>
<tr>
<td>Rugino 2003</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 6. Quality of placebo-controlled trials in children

#### Internal Validity

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross-Tsur 1997</td>
<td>Non-random assignment. Methods for assignment NR</td>
<td>NA</td>
<td>n/a-crossover</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR, NR, NR, NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Tourette's Disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sverd 1992</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR, NR, NR, NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Mental Retardation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varley 1982</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No/No</td>
</tr>
<tr>
<td>Gadow 1992</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR, NR, NR, NR</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
### Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross-Tsur 1997</td>
<td>Yes</td>
<td>No</td>
<td>Poor</td>
<td>NR/NR/30</td>
<td>NR</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Tourette's Disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sverd 1992</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/11</td>
<td>Children who were believed to be too severely ill, psychotic, or mentally retarded (IQ &lt; 75), or who had a seizure disorder, major organic brain dysfunction, major medical illness, medical or other contraindication to medication (other than tics), or pervasive developmental disorder</td>
<td></td>
</tr>
<tr>
<td>Mental Retardation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varley 1982</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>15/10/10</td>
<td>Psychotic disorders, undersocialized aggressive conduct disorders</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Gadow 1992</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/11</td>
<td>Children who were believed to be too severely ill; tics were the major clinical management concern; psychotic or mentally retarded (IQ &lt; 75); seizure disorder; major organic brain dysfunction; major medical illness, medical or other contraindication to medication, or pervasive developmental disorder</td>
<td>NR/NR</td>
</tr>
</tbody>
</table>
# Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross-Tsur 1997</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Yes for epilepsy+ADHD populations</td>
</tr>
<tr>
<td><strong>Tourette’s Disorder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sverd 1992</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Mental Retardation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varley 1982</td>
<td>80% naïve</td>
<td>Yes</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Gadow 1992</td>
<td>Unclear</td>
<td>Yes</td>
<td>Tourette Syndrome Association and NIMH grants; CIBA supplied MPH and placebo</td>
<td>Yes</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>-------------------------</td>
<td>---------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Gadow 1995</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Handen 1990</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Handen 1991</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Handen 1992</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadow 1995</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/34</td>
<td>Children who were believed to be too severely ill; tics were the major clinical management concern; psychotic or mentally retarded (IQ &lt; 75); seizure disorder; major organic brain dysfunction; major medical illness, medical or other contraindication to medication, or pervasive developmental disorder</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Handen 1990</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/12</td>
<td>NR</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Handen 1991</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/27</td>
<td>Severe motor deficits; use of other medication (anticonvulsants, antipsychotics); diagnosis of major depression or psychosis</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Handen 1992</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/14</td>
<td>NR</td>
<td>NR/NR</td>
</tr>
</tbody>
</table>
### Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadow 1995</td>
<td>Unclear</td>
<td>Yes</td>
<td>Tourette Syndrome Association and NIMH grants; CIBA supplied MPH and placebo</td>
<td>Yes</td>
</tr>
<tr>
<td>Handen 1990</td>
<td>Unclear</td>
<td>Yes</td>
<td>Edith L. Trees Foundation and Research Advisory Committee of Children's Hospital of Pittsburgh</td>
<td>Yes</td>
</tr>
<tr>
<td>Handen 1991</td>
<td>No</td>
<td>Yes</td>
<td>National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation; Research Advisory Committee of Children's Hospital of Pittsburgh</td>
<td>Yes</td>
</tr>
<tr>
<td>Handen 1992</td>
<td>No</td>
<td>Yes</td>
<td>National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation; Research Advisory Committee of Children's Hospital of Pittsburgh</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Evidence Table 6. Quality of placebo-controlled trials in children

*Internal Validity*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen 1994</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR, NR, NR, NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Handen 1995</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR, NR, NR, NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Handen 1996</td>
<td>NR</td>
<td>Inadequate - hospital pharmacist</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR, NR, NR, NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Handen 1997</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No</td>
</tr>
<tr>
<td>Handen 1999</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No</td>
</tr>
<tr>
<td>Handen 2000</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR, NR, NR, NR</td>
<td>Unclear</td>
</tr>
<tr>
<td>Agarwal 2001</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
<td>No</td>
</tr>
</tbody>
</table>
## Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
<th>Run-in/Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen 1994</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/47</td>
<td>NR</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Handen 1995</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/22</td>
<td>Diagnosis of autism or pervasive developmental disorder</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Handen 1996</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/44</td>
<td>Autism or pervasive developmental disorder</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Handen 1997</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/52</td>
<td>Autism or pervasive developmental disorder</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Handen 1999</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/11</td>
<td>Autism or pervasive developmental disorder</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Handen 2000</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/13</td>
<td>NR</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Agarwal 2001</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/10</td>
<td>NR</td>
<td>NR/NR</td>
</tr>
</tbody>
</table>
## Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year Country</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Handen 1994</td>
<td>No</td>
<td>Yes</td>
<td>National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation; Research Advisory Committee of Children's Hospital of Pittsburgh</td>
<td>No</td>
</tr>
<tr>
<td>Handen 1995</td>
<td>No</td>
<td>Yes</td>
<td>National Institute of Child Health and Human Development; US DHHS; Edith L. Trees Foundation</td>
<td>Yes</td>
</tr>
<tr>
<td>Handen 1996</td>
<td>No</td>
<td>Yes</td>
<td>National Institute of Child Health and Human Development; US DHHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Handen 1997</td>
<td>No</td>
<td>Yes</td>
<td>National Institute of Child Health and Human Development; US DHHS</td>
<td>Yes</td>
</tr>
<tr>
<td>Handen 1999</td>
<td>No</td>
<td>Yes</td>
<td>Fanny Pushin Rosenberg Research Foundation</td>
<td>Yes</td>
</tr>
<tr>
<td>Handen 2000</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fanny Pushin Rosenberg Research Foundation</td>
<td>Yes</td>
</tr>
<tr>
<td>Agarwal 2001</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
</tr>
</tbody>
</table>
## Evidence Table 6. Quality of placebo-controlled trials in children

### Internal Validity

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein 1988</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Unblinded study</td>
<td>Yes</td>
<td>NR, NR, NR, NR</td>
<td>None</td>
</tr>
<tr>
<td>Zeiner 1999 Fair</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR, NR</td>
<td>No</td>
</tr>
<tr>
<td>Sleator 1974</td>
<td>n/a - nonrandomized</td>
<td>n/a - nonrandomized</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR, NR, NR, NR, NR</td>
<td>NR</td>
</tr>
<tr>
<td>Arnold 2004 Poor</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR, NR</td>
<td>No</td>
</tr>
</tbody>
</table>
## Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein 1988</td>
</tr>
<tr>
<td>Zeiner 1999</td>
</tr>
<tr>
<td>Sleator 1974</td>
</tr>
<tr>
<td>Arnold 2004</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair</td>
</tr>
<tr>
<td>Poor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Withdrawal of medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat (ITT) analysis</td>
</tr>
<tr>
<td>Post-randomization exclusions</td>
</tr>
<tr>
<td>Quality Rating</td>
</tr>
<tr>
<td>Number screened/eligible/enrolled</td>
</tr>
<tr>
<td>Exclusion criteria</td>
</tr>
<tr>
<td>Run-in/Washout</td>
</tr>
</tbody>
</table>

### Klein 1988
- No
- No
- Poor
- NR/NR/62
- NR
- NR/NR

### Zeiner 1999
- Yes
- No
- Fair
- NR/NR/21
- NR
- NR/NR

### Sleator 1974
- NR
- NR
- Poor
- NR/NR/42
- NR
- NR/NR

### Arnold 2004
- No
- No
- Fair
- 116/89/89
- Cardiovascular, renal, respiratory (other than asthma/allergy), endocrine, or immune system disease; history of substance abuse; hypersensitivity to d,l-MH or other stimulants; treatment with any investigational drug within 30 days of screening; other significant central nervous system disorders; and treatment with antidepressants, neuroleptics/antipsychotics, mood stabilizers, anticonvulsants, beeta blockers, alpha-2 agonists, other stimulants, thyroid medications, chronic oral steroids, or sedatives/hypnotics
- NR/NR

---

Pharmacologic Treatments for ADHD  Page 410 of 616
## Evidence Table 6. Quality of placebo-controlled trials in children

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klein 1988</td>
<td>NR</td>
<td>Yes</td>
<td>Supported in part by Public Health Service grant MH 18579</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zeiner 1999 Fair</td>
<td>Unclear</td>
<td>Yes</td>
<td>Norwegian Medical Research Council, Norwegian Public Health Association, and the Legacy of Haldis and Josef</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sleator 1974</td>
<td>NR</td>
<td>Yes</td>
<td>NIMH grant; MPH supplied by Ciba-Geigy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Arnold 2004 Poor</td>
<td>Unclear</td>
<td>Yes</td>
<td>Celgene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Eligibility criteria</td>
<td>Comorbidity</td>
<td>Interventions and total daily dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conrad</td>
<td>children from low-income neighborhood, in grades kindergarten-second grade, with rating from teacher as hyperactive (19th percentile or lower), and with signs 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</td>
<td>NR</td>
<td>n=68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1971</td>
<td></td>
<td></td>
<td>randomized into 1 of 4 groups:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td>Grp A: placebo/no tutoring (n=18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grp B: placebo/tutoring (n=17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grp C: dextroamphetamine/no tutoring (n=17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grp D: dextroamphetamine/tutoring (n=16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>duration 4-6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>doses increased/decreased at 5mg/day, until undesirable side effects, or maximum positive response achieved. Average dose: 10-20 mg/day.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible enrolled</th>
<th>Number withdrawn/lost to fu</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conrad</td>
<td>1971</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>1350/262/106/68</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>(Quality) Placebo-Controlled Trials (&gt;= 6 Months Duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conrad</td>
<td>1971</td>
<td>(Poor)</td>
</tr>
</tbody>
</table>

**Mean difference scores between baseline and post-testing**

- reported as variable: grp A (placebo/no tutor); grp B (placebo/tutor);
  - grp C (dextroamphetamine/no tutor); grp D (dextroamphetamine/tutor); (p-Value)

<table>
<thead>
<tr>
<th>Motor Coordination</th>
<th>.17; 24; 18; .25; (.20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeating a Motor Pattern</td>
<td>.00; 1.00; .71; 1.50; (.02)</td>
</tr>
<tr>
<td>Visual Tracking</td>
<td>.00; 59; .18; .31; (.12)</td>
</tr>
<tr>
<td>Motor Activity</td>
<td>-.06; .18; .65; .69; (.01)</td>
</tr>
<tr>
<td>Distractibility</td>
<td>.22; .35; .59; .44; (.50)</td>
</tr>
<tr>
<td>Hyperkinetic Score</td>
<td>2.28; 5.59; 9.29; 6.25; (.08)</td>
</tr>
<tr>
<td>Behavior Rating By Teacher</td>
<td>3.00; 2.77; 2.59; 2.19; (.001)</td>
</tr>
<tr>
<td>Behavior Rating By Parent</td>
<td>2.94; 2.77; 2.06; 1.94; (.001)</td>
</tr>
<tr>
<td>Spatial Orientation</td>
<td>1.33; 1.65; .71; 2.00; (.50)</td>
</tr>
<tr>
<td>Koppitz Errors</td>
<td>1.44; 2.18; 3.06; 4.25; (.07)</td>
</tr>
<tr>
<td>Frostig I</td>
<td>-.56; -.18; .53; -.25; (.30)</td>
</tr>
<tr>
<td>Frostig II</td>
<td>-.39; .18; 1.00; .00; (.12)</td>
</tr>
<tr>
<td>Frostig III</td>
<td>.06; 1.29; 1.47; 1.69; (.25)</td>
</tr>
<tr>
<td>Frostig IV</td>
<td>-.56; -.47; 1.18; .31; (.02)</td>
</tr>
<tr>
<td>Frostig V</td>
<td>-.53; 1.00; .69; (.02)</td>
</tr>
<tr>
<td>Frostig PQ</td>
<td>-.461; 2.18; 10.41; .69; (.02)</td>
</tr>
<tr>
<td>Frostig Stars</td>
<td>.56; .53; .88; .56; (.50)</td>
</tr>
</tbody>
</table>

**WISC Subtests**

<p>| Information | -.17; .88; -.06; 1.06; (.005) |
| 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) |</p>
<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conrad</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Evidence Table 7. Long-term efficacy trials**

**Placebo-Controlled Trials (≥6 Months Duration)**

**DEX**

Conrad 1971 (Poor)
<table>
<thead>
<tr>
<th>Author</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH</td>
<td>Children had to meet DSM-III-R criteria for ADHD, based on a) Conners Parent and Teacher Hyperkinesis Indices scores &gt;=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.</td>
<td>Original study of n=107: Conduct disorder: 7.5% (n=8) Oppositional defiant disorder: 43.0% (n=46)</td>
<td>All MPH and behavioral treatments had been discontinued 9 months prior to follow-up.</td>
</tr>
<tr>
<td>Ialongo</td>
<td></td>
<td></td>
<td>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</td>
</tr>
</tbody>
</table>
## Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Quality</th>
<th>MPH</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ialongo</td>
<td>1993</td>
<td>Fair</td>
<td>117/107/96</td>
<td>8.27 years</td>
<td>Male = 77.4%</td>
<td>White = 84.9%</td>
<td>NR</td>
<td>18/7/71 analyzed</td>
</tr>
</tbody>
</table>
**Evidence Table 7. Long-term efficacy trials**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>(Quality)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH</td>
<td>1993</td>
<td>Fair</td>
<td>Overall trend (the exception was the parent report data) towards an erosion of treatments gains seen across treatments.</td>
</tr>
<tr>
<td>Ialongo</td>
<td></td>
<td></td>
<td>(&quot;A table of means and standard deviations by condition and over time for each of the outcome measures is available from the senior author.&quot;)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Only significant contrast seen for PT+SC treatment effect for posttest to follow-up (fu) : $F[5,56]=3.69$, $p=0.006$.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Univariate $F$ for PT+SC treatment effect was significant for each of the parent report measures:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPRS, $F[1,64]=14.31$, $p&lt;0.001$; SNAP, $F[1,62]=4.89$, $p=0.031$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CBCL total problems, $F[1,61]=12.03$, $p=0.001$; CBCL externalizing $F[1,61]=11.07$, $p=0.001$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CBCL aggression $F[1,60]=6.29$, $p=0.015$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 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).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Multivariate $F$s for pretest to posttest and postest to fu contrasts were significant for medication by period effect:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pretest to posttest:$F[4,120]=5.05$, $p=0.001$; posttest to fu: $F[4,121]=3.37$, $p=0.012$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Univariate $F$s for off-task behavior:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pretest to posttest:$F[2,62]=10.36$, $p&lt;0.001$; posttest to fu: $F[2,60]=7.18$, $p=0.002$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Children receiving stimulant medication showed a significantly greater deterioriation in posttest to fu scores than did children receiving placebo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(explanation: the non-medicated children showed virtually no change pretest to posttest or postest to fu, whereas medicated children did show significant improvement from pretest to posttest and deterioration of those gains from posttest to fu.)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(no data given)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- No evidence of greater maintenance of treatment gains at fu were found with children receiving PT+SC+medication. (no data given).</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Method of adverse effects</td>
<td>Adverse Effects Reported</td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
<td>---------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Ialongo</td>
<td>1993</td>
<td>NR for follow-up group</td>
<td>NR for follow-up group</td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td>AE details not specified for short-term group, though 3 withdrew because of them and 13 dropped out &quot;owing to concerns about the medication, or insufficient time to attend the groups, or dissatisfaction with treatment efficiency&quot;.</td>
</tr>
</tbody>
</table>
## Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
<th>Duration</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupietz</td>
<td>Children between 7 and 13 inclusive, with an IQ &gt;= 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 &gt;= 2 years, a teacher rating of &gt;= 2.5 (on a 1 to 4 scale) on the Hyperactivity factor of the Conner's TRS. Children with an additional Axis I psychiatric diagnosis or uncorrected hearing or visual deficits were excluded.</td>
<td>Developmental Reading Disorder</td>
<td>0.3 mg/kg, 0.5 mg/kg, 0.7 mg/kg or placebo per day</td>
<td>Duration was a total of 28 weeks: 14 weeks of treatment, 1 wk placebo, 12 wks treatment, 1 wk placebo</td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupietz</td>
<td>1987</td>
<td>Mean age = 9.7 years</td>
<td>Male = NR</td>
<td>White = NR</td>
<td>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</td>
<td>NR/NR/58</td>
<td>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</td>
</tr>
</tbody>
</table>

NR/NR/58 before completing the 28-week drug protocol/NR/47, but sample size varies across dependent measures due to missing forms from parents or teachers.
### Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupietz</td>
<td>1987</td>
<td>Conners TRS scores with the adjusted means for Agressiveness (I), Inattentiveness (II), and Hyperactivity (IV) Factors analyzed together:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Post-hoc analysis: 0.7 mg/kg group received significantly lower ratings than placebo (p=NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean ratings for week (all dosages combined): week 2, week 14, week 27: 1.96, 1.89, 2.05*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*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).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Post-hoc Analysis: only 0.7mg and placebo roops were found to differ significantly (p-value NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCB Scale: Mean parent ratings for weeks 2, 14, 27 (all dose groups combined): 185.6, 180.0, 132.2*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WWPAS: No dose group effects were obtained; the main effect for weeks only approached significance as a main effect (p=0.058).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean activity ratings for weeks 2, 14, 27 (all dosages combined) were 18.5, 16.5, 16.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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&lt;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).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STM Task: no drug effects were obtained on latency of correct response measure; thus, these data not reported.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A main effect of matrix (F=51.51, p&lt;0.001) and a significant interaction between dose group and study week (F=3.68, p&lt;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).</td>
</tr>
</tbody>
</table>
## Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupietz</td>
<td>NR</td>
<td>NR</td>
<td>11 withdrawals; study states that some withdrew due to side effects, but does not give a specific number</td>
</tr>
<tr>
<td>1987</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Evidence Table 7. Long-term efficacy trials**

<table>
<thead>
<tr>
<th>Author</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTA Cooperative Group 1999. 2004</td>
<td>Children between 7 and 9.9 years (grades 1-4), in residence with same primary caretaker &gt;=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. Exclusion criteria: situations that would prevent families' full participation in assessments or treatment, or that might require additional treatment incompatible with study treatments (ex. child currently in hospital, child currently in another study, child with =&lt;80 on all WISC-III scales and SIB, bipolar disorder, psychosis, or personality disorder, chronic serious tics or Tourette syndrome, OCD serious enough to require separate treatment, neuroleptic medication in previous 6 months, major neurological or medical illness, history of intolerance to MTA medications, ongoing or previously unreported abuse, parental stimulant abuse in previous 2 years, same classroom as child already in MTA study, non-English-spea</td>
<td>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)</td>
<td>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 maintenatnce dose. -MM and CT subjects originally given MPH: 77.3% (n=198 of 256 who completed titration) MM and CT subjects originally given dex: 10.2% (n=26) MM and CT subjects originally given no medication: 12.5% (n=32) average initial dose of MPH = 30.5 mg/day -At the end of 14 months, MM and CT subjects taking MPH: 73.4% (n=212 of 289 completing both MM and CT) MM and CT subjects taking dex: 10.4% (n=30) MM and CT subjects on other drugs: 3.1% (n=9) MM and CT subjects on no medication: 13.1% (n=38) CT subjects received 31.2 mg of MPH versus MM=37.7 mg of MPH -At the end of 14 months, CC subjects taking MPH: 57.5% (n=84 of 146 CC subjects) CC subjects taking dex: not specified CC subjects on other drugs: 16.4% (n=24) CC subjects on no medication: not specified Mean total daily dose for CC subjects=22.3 mg of MPH at treatment 14 Month Duration for all treatment arms</td>
</tr>
</tbody>
</table>
## Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTA Cooperative</td>
<td>1999-2004</td>
<td>Mean Age = 8.5 (range: 8.4-8.6) years</td>
<td>Male = 80.3% (n=465)</td>
<td>White = 60.6%</td>
<td>WISC-III IQ, mean score = 100.9</td>
<td>4541/609/579</td>
<td>NR/NR/526 (number gotten from test score subject numbers at 14 months)</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td>African American = 19.9%</td>
<td>Conners Teacher Rating Scale, mean score = 1.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hispanic = 8.3%</td>
<td>Conners Parent Rating Scale, mean score = 0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Welfare recipients = 19.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Subjects living with 2-parent family = 68.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td></td>
</tr>
<tr>
<td>(Quality)</td>
<td></td>
</tr>
<tr>
<td>ADHD Drug</td>
<td></td>
</tr>
<tr>
<td>Versus Non-Drug Treatment</td>
<td></td>
</tr>
<tr>
<td>MTA Cooperative Group</td>
<td>1999-2004</td>
</tr>
</tbody>
</table>

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>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 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTA Cooperative Group 1999. 2004</td>
<td>Side-effects were monitored monthly using parent-completed 13-item Pittsburgh Side Effects Rating Scale (ratings=not present, mild, moderate, severe)</td>
<td>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 severe side effects (depression, worrying, or irritability) could have been due to non-medication factors)</td>
<td>20 complete dropouts by 14 months = 3.5%; Withdrawals due to AE's: not specified</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Eligibility criteria</td>
<td>Comorbidity</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>MPH vs.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parent training</td>
<td>1986</td>
<td>Children aged 5-9 years, with DSM-III diagnosis of ADHD, and with rating of 1.5 or</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>higher on Teacher's Activity Index.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH vs. parent training</td>
<td>Firestone</td>
<td>Firestone 1986: ages: 5-9 yrs, gender: NR, ethnicity: NR</td>
<td>NR</td>
<td>NR/NR/73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR/ 21 lost to fu/ 52 analyzed for entire 2 yr period</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MPH vs. parent training</strong></td>
<td></td>
</tr>
<tr>
<td>Firestone 1986</td>
<td>Results at 3 mos: (mean scores; SD; n)</td>
</tr>
<tr>
<td></td>
<td>Hyperactivity Index: MED: 0.81; .44; (n=11); PTPL: 1.12; .56; (n=9); PTMED: 1.03; .46; (n=10)</td>
</tr>
<tr>
<td></td>
<td>Conduct Problems: MED: 6.45; 4.42; (n=11); PTPL: 6.89; 4.23; (n=9); PTMED: 5.8; 2.81; (n=10)</td>
</tr>
<tr>
<td></td>
<td>Reaction Time: MED: .64; .19; (n=12); PTPL: .75; .22; (n=8); PTMED: 5.8; 2.81; (n=10)</td>
</tr>
<tr>
<td></td>
<td>Verbal Grade: MED: 3.42; 1.54; (n=10); PTPL: 2.51; 1.62; (n=8); PTMED: 3.36; 1.22; (n=9)</td>
</tr>
<tr>
<td><strong>Test scores at 3 mos: (mean scores; SD; n)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperactivity Index: MED: 0.96; .59; (n=11); PTPL: 1.07; .55; (n=9); PTMED: .92; .36; (n=10)</td>
</tr>
<tr>
<td></td>
<td>Conduct Problems: MED: 5.91; 3.61; (n=11); PTPL: 6.44; 4.02; (n=9); PTMED: .92; .36; (n=10)</td>
</tr>
<tr>
<td></td>
<td>Reaction Time: MED: .59; .13; (n=12); PTPL: .70; .15; (n=8); PTMED: .63; .25; (n=10)</td>
</tr>
<tr>
<td></td>
<td>Verbal Grade: MED: 3.56; 1.62; (n=10); PTPL: 3.23; 2.16; (n=8); PTMED: 3.97; 1.34; (n=9)</td>
</tr>
<tr>
<td><strong>Test Scores at 10-12 mos: (mean scores; SD; n)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperactivity Index: MED: 1.09; .60; (n=11); PTPL: 1.09; .63; (n=9); PTMED: 1.06; .59; (n=10)</td>
</tr>
<tr>
<td></td>
<td>Conduct Problem: MED: 6.97; 4.41; (n=11); PTPL: 4.51; 3.57; (n=9); PTMED: 1.06; .59; (n=10)</td>
</tr>
<tr>
<td></td>
<td>Reaction Time: MED: .60; .11; (n=12); PTPL: .64; .14; (n=8); PTMED: .52; .12; (n=10)</td>
</tr>
<tr>
<td></td>
<td>Verbal Grade: MED: 4.56; 1.70; (n=10); PTPL: 4.29; 2.74; (n=8); PTMED: 5.14; 1.92; (n=9)</td>
</tr>
<tr>
<td>Author</td>
<td>Method of adverse effects</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Firestone</td>
<td>report of symptoms from teachers.</td>
</tr>
</tbody>
</table>

**Evidence Table 7. Long-term efficacy trials**
### Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Eligibility criteria</th>
<th>Comorbidity</th>
<th>Interventions and total daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>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 &gt;=12 months prior to referral), symptoms associated with ADHD. Parent and teacher interviews were conducted to ascertain the child's symptoms and emotional climate in the home after health care or special education personnel referred the boy to the study. Each boy also demonstrated a reading deficit of at least two grade levels. Excluded were boys with symptoms that seemed to stem from stress at home or from inconsistent child management practices; with major diseases; with obvious physical defects; with gross neurological, sensory, or motor impairment; or with psychosis.</td>
<td>Reading deficits</td>
<td>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 &quot;duration of study&quot;</td>
</tr>
</tbody>
</table>
### Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics (mean scores)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>1985</td>
<td>Mean age = 11.36 years</td>
<td>Male = 100%</td>
<td>Ethnicity NR</td>
<td>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)</td>
<td>NR/NR/40</td>
<td>NR/NR/40</td>
</tr>
</tbody>
</table>

Since 10 boys were non-random, a one-way multiple ANOVA was performed on pre-treatment scores; result was nonsignificant F ratio, F(3,36)=0.47, n.s.; these results indicate equality prior to treatment between subgroups.
### Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>1985</td>
</tr>
</tbody>
</table>

F ratios determined using separate MANOVAs to determine differences in the effectiveness of treatment and to determine the persistence of each treatment at delayed posttesting (DPT):

- MPH only: Combined: CTO: No Treatment
  - F(2,34)=3.95, p<0.001; F(2,34)=5.06, p<0.0001; F(2,34)=1.88, p<0.69; F(2,34)=0.53, p<0.95

**Comparisons of Univariate Measures by Condition**

*p-values* for: MPH only; Combined Therapy; Cognitive Training only (CTO); and No Treatment

- CCT Omissions: p<0.0001; p<0.0001; p<0.07 (as); ns
- CCT Comissions: ns; p<0.08 (as); ns
- 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
- CFFT 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
- Conners Parent: p<0.05; p<0.002; ns
- Teacher Rating Attention: p<0.005; p<0.05; 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

*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 between posttest and DPT were ns (no p-value given).

**Canonical correlation coefficients (R²) for the multivariate analyses for MPH Only; Combined; CTO**

- 0.963; 0.971; 0.926 (amount of variance in dependent measures across pre-, post-, and DPT accounted for by the differences in MPH only and Combined treatments was virtually the same).
### Evidence Table 7. Long-term efficacy trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Method of adverse effects</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals; withdrawals due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>1985</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 8. Quality in long-term efficacy trials

**Internal Validity**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Conrad 1971</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
</tr>
<tr>
<td>Brown 1985</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>NR, NR, NR, NR</td>
</tr>
<tr>
<td>Kupietz 1987</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
</tr>
<tr>
<td>Ialongo 1993</td>
<td>NR</td>
<td>NR</td>
<td>No, more non-white children in placebo group</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
</tr>
</tbody>
</table>
**Evidence Table 8. Quality in long-term efficacy trials**

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Loss to follow-up: differential/high</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conrad 1971</td>
<td>No/No</td>
<td>No</td>
<td>NR</td>
<td>Poor</td>
<td>NR/96/96</td>
<td>NR</td>
</tr>
<tr>
<td>Brown 1985</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Poor</td>
<td>NR/NR/40</td>
<td>Gross neurological, sensory, or motor impairment or psychosis</td>
</tr>
<tr>
<td>Kupietz 1987</td>
<td>No/No</td>
<td>No, sample size varied across dependent measures, based on incomplete data</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/58</td>
<td>Additional Axis I psychiatric diagnosis or uncorrected hearing or visual deficits</td>
</tr>
<tr>
<td>Ialongo 1993</td>
<td>No/No</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td>117/107/96</td>
<td>Comorbid anxiety and/or depressive disorder; gross physical impairments, intellectual deficits or psychosis</td>
</tr>
<tr>
<td>Author, Year, Country</td>
<td>Run-in/Washout</td>
<td>Class naïve patients only?</td>
<td>Control group standard of care</td>
<td>Funding</td>
<td>Relevance</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------</td>
<td>---------------------------</td>
<td>-------------------------------</td>
<td>---------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>Conrad 1971</td>
<td>NR/NR</td>
<td>NR</td>
<td>Yes</td>
<td>NY State Department of Mental Hygiene Contract No. C36725</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Brown 1985</td>
<td>NR/NR</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Kupietz 1987</td>
<td>NR/NR</td>
<td>NR</td>
<td>Yes</td>
<td>NIMH grant MH 36004</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Ialongo 1993</td>
<td>NR/NR</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 8. Quality in long-term efficacy trials

*Internal Validity*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MTA</td>
<td>NR</td>
<td>Yes</td>
<td>No, significant differences across treatment groups in age</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes, Yes, Yes, Yes</td>
</tr>
<tr>
<td>Firestone 1986</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes, NR, NR, NR</td>
</tr>
</tbody>
</table>
## Evidence Table 8. Quality in long-term efficacy trials

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Loss to follow-up: differential/high</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTA</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
<td>4541/609/579</td>
<td>ex. child currently in hospital, child currently in another study, child with =&lt;80 on all WISC-III scales and SIB, bipolar disorder, psychosis, or personality disorder, chronic serious tics or Tourette syndrome, OCD serious enough to require separate treatment, neuroleptic medication in previous 6 months, major neurological or medical illness, history of intolerance to MTA medications, ongoing or previously unreported abuse, parental stimulant abuse in previous 2 years, same classroom as child already in MTA study, non-English-speaking primary caretaker, no telephone, suicidal or homicidal, another child in same household in MTA study</td>
</tr>
<tr>
<td>Firestone 1986</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
<td>NR/NR/73</td>
<td>Definite signs of brain damage, epilepsy, or psychosis</td>
</tr>
</tbody>
</table>
### Evidence Table 8. Quality in long-term efficacy trials

<table>
<thead>
<tr>
<th>Author, Year, Country</th>
<th>Run-in/Washout</th>
<th>Class naïve patients only?</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTA</td>
<td>NR/NR</td>
<td>No</td>
<td>Yes</td>
<td>NIMH grants</td>
<td>Yes</td>
</tr>
<tr>
<td>Firestone 1986</td>
<td>NR/NR</td>
<td>NR</td>
<td>Yes</td>
<td>Ontario Ministry of Health grants</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Study Design</th>
<th>Setting</th>
<th>Eligibility criteria</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Run-in/ Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion SR vs methylphenidate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuperman, 2001</td>
<td>U.S. (Fair)</td>
<td></td>
<td></td>
<td>DB RCT</td>
<td>parallel groups</td>
<td>Patients were recruited from the community through newspaper ads. Subjects were required to meet DSM-IV criteria for ADHD at time of study, have a chronic course of ADHD symptoms from childhood to adulthood, and have moderate or severe impairment due to ADHD symptoms.</td>
<td>Methylphenidate was titrated over 1 week to a maximum dose of 0.9 mg/kg/day, administered at 8AM, noon, and 4 PM. Bupropion SR was titrated over 2 weeks to a maximum of 300 mg/day as follows: 200 mg at 8AM and 100 mg at 4PM, with placebo taken at noon. Placebo tid: 8AM, noon, 4 PM.</td>
<td>7-day placebo lead-in; Washout NR</td>
<td></td>
</tr>
<tr>
<td><strong>Dextroamphetamine vs guanfacine</strong></td>
<td></td>
<td></td>
<td></td>
<td>DB RCT, crossover study</td>
<td></td>
<td>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.</td>
<td>Daily dosing was qd on awakening, beginning with 1 capsule (containing either lactose, 0.05 mg guanfacine, or 2.5 mg DAMP) and increased by an additional capsule every day to 2 days as tolerated. DAMP maximum 20 mg/day, mean 10.2 mg/day Guanfacine maximum 2.0 mg/day, mean 1.10 mg/day Placebo 2-week treatment phases of placebo, guanfacine, and dextroamphetamine (DAMP) were separated by 4-day washouts</td>
<td>Run-in NR; 4-day washouts between treatments</td>
<td></td>
</tr>
</tbody>
</table>

NR = Not reported
## Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion SR vs methylphenidate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuperman, 2001</td>
<td></td>
<td>U.S.</td>
<td>(Fair)</td>
<td>CGI Severity; CGJ Improvement, with response defined as a score of 1 (very much improved) or 2 (much improved) ADHDRS-self; HAM-D, HAM-A; Neuropsychological assessments: HVLT, Digit Ordering Test, Trails A &amp; B; Verbal Fluency; Conners’ CPT</td>
<td>Mean age 32.4</td>
<td>70% male</td>
<td>Ethnicity NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean years of education: 15.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR/NR/37</td>
<td></td>
<td></td>
<td>N enrolled in each group not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dextroamphetamine vs guanfacine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean age 41.2</td>
<td>41% male</td>
<td>Ethnicity NR</td>
<td></td>
</tr>
<tr>
<td>Taylor, 2001</td>
<td></td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Five self-administered rating scales at baseline and on the last day of each treatment phase within 4 hrs of last dose: 2 scales for ADHD (DSM-IV ADHD behavior checklist for adults, and CSCA, and one scale each for depression, anxiety, and OCD: BDI, Ham-A, Y-BOCS. Patients also self-assessed task motivation, and how long medication effects lasted. Cognition tests: Stroop Color-World Interference Test, and CFL version of COWAT.</td>
<td>100% completed high school; 23% completed college; 12% completed postgraduate degrees</td>
<td>70% had family history of ADHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR/NR/17</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NR = Not reported**
# Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion SR vs methylphenidate</td>
<td></td>
<td></td>
<td>Kuperman, 2001 U.S. (Fair)</td>
<td>7 (18.9%) withdrew, 5 before and 2 after randomization; 0 lost to fu; 30 (81%) analyzed: bupropion n=11 methylphenidate n=8 placebo n=11</td>
</tr>
<tr>
<td>Dextroamphetamine vs guanfacine</td>
<td></td>
<td></td>
<td>Taylor, 2001 U.S. (Fair)</td>
<td>No withdrawals; No loss to followup; 17 analyzed, all exposed to both DAMP &amp; guanfacine</td>
</tr>
</tbody>
</table>
### Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion SR vs methylphenidate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuperman, 2001</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Bupropion vs methylphenidate vs placebo, mean change in score:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADHDRS-self -13.7 vs -10.1 vs -12.4 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HAM-D -1.5 vs -0.1 vs -2.9 (ns); HAM-A -3.6 vs -3.3 vs -3.1 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% CGI responders 64% vs 50% vs 27% (ns for comparison between drug and placebo)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neuropsychological assessment, mean change in score:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HVLT immediate recall +3.5 vs +2.0 vs -0.2 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HVLT delayed % 0.0 vs 0.0 vs -0.1 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cooper digit ordering +7.2 vs +4.5 vs +3.5 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trails A -5.4 vs -2.1 vs -8.1 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trails B -5.0 vs -9.5 vs -9.8 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Verbal fluency +6.5 vs +7.1 vs +1.1 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPT attentiveness +0.1 vs +0.8 vs +0.2 (ns)</td>
<td></td>
</tr>
</tbody>
</table>

**Dextroamphetamine vs guanfacine**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor, 2001</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>DAMP vs guanfacine:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration of action 5.4 vs. 6.9 hours (p=0.006)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increased task motivation reported by 16 vs. 0 patients (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Means for study measures:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Copeland 66.5 vs 68.4 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Beck depression 12.4 vs 12.8 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hamilton rating scale for anxiety 12.8 vs 10.8 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Y-BOCS obsessions 4.5 vs 4.4 (ns); compulsions 3.7 vs 2.3 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cognitive: COWAT 79.5 vs 72.8 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug preference: 12 chose DAMP (citing positive effect on motivation compared with guanfacine); 4 chose guanfacine; 1 chose placebo</td>
<td></td>
</tr>
</tbody>
</table>

NR = Not reported
### Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals by treatment; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuperman, 2001</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Bupropion SR vs methylphenidate</td>
<td>Elicited by investigator</td>
<td>Insomnia: 15.4% in bupropion, 16.7% in methylphenidate</td>
<td>Withdrawals by treatment group unknown; Due to AEs: 2 in methylphenidate, 1 in placebo</td>
<td>At end of each treatment phase, subjects completed a rating scale for side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Also in bupropion: dry mouth 30.7%, 15.4% headache, 15.4% insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Also in methylphenidate: 25% appetite suppression, 16.7% tremor, 16.7% sweating, 16.7% jitteriness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For placebo: 16.7% tiredness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor, 2001</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Dextroamphetamine vs guanfacine</td>
<td>At end of each treatment phase, subjects completed a rating scale for side effects</td>
<td>Muscle tension 5 (29.4%) on DAMP Fatigue 4 (23.5%) on guanfacine</td>
<td>0 withdrawals</td>
<td>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.</td>
</tr>
</tbody>
</table>

NR = Not reported
### Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Study Design, Setting</th>
<th>Eligibility criteria</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Run-in/ Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine vs modafinil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor, 2000 U.S. (Fair)</td>
<td>DB RCT, crossover study</td>
<td>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.</td>
<td>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.</td>
<td>Run-in NR; 4-day washout between treatments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR = Not reported
### Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Other population characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor, 2000</td>
<td>U.S.</td>
<td>Fair</td>
<td>Dextroamphetamine vs modafinil</td>
<td>At baseline and on the last day of each treatment phase within 3 hours of the last dose: self-rated ADHD behavior checklist for adults; self-rated BDI; clinician-administered Ham-A. Clinician-administered cognitive tests: letters C, F, and L of the COWAT; Wechsler Adult Intelligence Scale-Revised; Stroop-Color-Word Interference Test</td>
<td>Mean age 40.8</td>
<td>59% male</td>
<td>NR</td>
<td>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</td>
</tr>
</tbody>
</table>

NR = Not reported
### Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine vs modafinil</td>
<td>Taylor, 2000</td>
<td>U.S. (Fair)</td>
<td>1 withdrawn</td>
<td></td>
</tr>
<tr>
<td></td>
<td>U.S.</td>
<td>(Fair)</td>
<td>0 lost to fu;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21 analyzed, all exposed to both DAMP &amp; modafinil</td>
<td></td>
</tr>
</tbody>
</table>

NR = Not reported
### Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dextroamphetamine vs modafinil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor, 2000</td>
<td>U.S. (Fair)</td>
<td>Cognitive mean scores, DAMP vs modafinil:</td>
<td>COWAT Test 86.5 vs 87.7 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Digit Span forward 10.3 vs 10.3 (ns); backward 7.6 vs 7.5 (ns)</td>
<td>Stroop Color 50.2 vs 48.0 (ns); Word 48.8 vs 48.8 (ns); Color-Word 52.0 vs 51.6 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSM-IV ADHD behavior checklist mean scores, DAMP vs modafinil:</td>
<td>Total 20.0 vs 18.3 (ns); Hyperactivity subscore 9.0 vs 7.3 (ns); Inattention subscore 11.0 vs 10.5 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug preference: 48% chose DAMP, 43% chose modafinil, 10% chose placebo</td>
<td>NR = Not reported</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals by treatment; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor, 2000</td>
<td></td>
<td>U.S.</td>
<td><strong>Dextroamphetamine</strong></td>
<td>Side effect checklist, elicited by investigator on the last visit of each drug trial</td>
<td>DAMP vs modafinil:</td>
<td>1 withdrew before receiving treatment; No withdrawals due to AEs</td>
<td>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.</td>
</tr>
<tr>
<td>(Fair)</td>
<td></td>
<td></td>
<td><strong>vs modafinil</strong></td>
<td></td>
<td>Insomnia 38 vs 19% (ns)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Irritability 14 vs 19% (ns)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Muscle tension 24 vs 19% (ns)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Appetite suppression 24 vs 19% (ns)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anxiety 19 vs 10% (ns)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Headaches 10 vs 10% (ns)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dizziness 10 vs 0% (ns)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lingual dyskinesia 5 vs 10% (ns)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Trial Name (Quality Score)</td>
<td>Study Design</td>
<td>Setting</td>
<td>Eligibility criteria</td>
<td>Interventions</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>---------</td>
<td>---------------------------</td>
<td>--------------</td>
<td>---------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Matochik, 1994</td>
<td></td>
<td>U.S.</td>
<td></td>
<td>DB, RCT</td>
<td></td>
<td>Subjects had to be adults who met following:</td>
<td>DAMP 5 mg/day, up to 5-15 mg/day OR methylphenidate 5 mg/day, up to 5-25 mg/day.</td>
</tr>
<tr>
<td>(Fair)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1) DSM-II criteria for ADHD</td>
<td>Duration: 6-15 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2) Utah criteria for attention deficit disorder in adulthood</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3) a childhood history of ADHD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4) no history of an other major psychiatric disorders.</td>
<td></td>
</tr>
</tbody>
</table>

NR = Not reported
### Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age Gender Ethnicity</th>
<th>Other population characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matochik, 1994</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Dextroamphetamine vs methylphenidate</td>
<td>PET scan, (schedule NR) &quot;How I Feel&quot; Questionnaire administered on PET scan days Subject's Treatment Emergent Symptom Scale (schedule NR) modified Conner's Parent Rating Scale for Spouse/Closed friend to complete (schedule NR) NIMH Clinical Global Impressions scale administered at end of study period.</td>
<td>mean age 35.5 y 21 males, 16 females Ethnicity NR</td>
<td>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</td>
</tr>
</tbody>
</table>

NR = Not reported
## Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Number withdrawn/lost to fu/analyzed</th>
</tr>
</thead>
</table>

NR = Not reported
### Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Trial Name (Quality Score)</th>
<th>Dextroamphetamine vs methyphenidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matochik, 1994</td>
<td>U.S. (Fair)</td>
<td>Behavioral Effects of methyphenidate vs d-amphetamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Conner's rating scale</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Self: 5.0; 0.0001 vs 4.6; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Spouse/Other: 5.7; 0.0001 vs 8.3; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&quot;How I Feel&quot; Questionnaire</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feel cranky or tired: 0.5; 0.02 vs NR; NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feel like keeping my mind on things: 0.5; 0.0001 vs 0.6; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feel restless, like moving around: 0.8; 0.0002 vs NR; NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feel things may get messed up today: 0.0; NR vs NR; NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feel I'm not much good at things: 0.3; 0.007 vs 0.2; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feel sad: NR; NR vs 2.2; 0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feel like I don't want to play with anyone: NR; NR vs 0.1; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feel in a good mood: NR; NR vs 2.2; 0.008</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feel like my thoughts are going fast: NR; NR vs 0.2; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feel tired and slow: NR; NR vs 0.0; NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subject's Treatment Emergent Symptom Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trouble with sitting still: 0.7; 0.0001 vs 0.7; 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Feeling sleepy: 0.4; 0.007 vs 0.2; 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not being happy: 0.3; 0.02 vs NR; NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trouble with paying attention: 0.4; 0.0001 vs 0.6; 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Colds or sniffles: NR; NR vs 0.1; 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headaches: NR; NR vs 0.2; 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tiredness: NR; NR vs 0.3; 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trouble getting or staying asleep: NR; NR vs 0.3; 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Getting along with parents: NR; NR vs 0.4; 0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Crying: NR; NR vs 0.1; 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Being sad: NR; NR vs 0.1; 0.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NR = Not reported
### Evidence Table 9. Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Trial Name</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
<th>Total withdrawals by treatment; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matochik, 1994</td>
<td>U.S. (Fair)</td>
<td>Dextroamphetamine vs methyphenidate</td>
<td>NR</td>
<td>1 subject reported adverse events (not specified) within first 2 weeks, and was immediately switched to other drug</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NR = Not reported**
### Evidence Table 10. Quality Assessment of Head to Head Trials in Adults with ADHD

#### Internal Validity

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion SR vs methylphenidate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuperman, 2001 U.S.</td>
<td>Method not reported</td>
<td>Method not reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes but method not described</td>
<td>Not reported</td>
<td>Yes</td>
</tr>
</tbody>
</table>

| **Dextroamphetamine vs guanfacine** | | | | | | | |
| Taylor, 2001 U.S. | Method not reported | Method not reported | Not reported | Yes | Yes but method not described | Not reported | Yes |

| **Dextroamphetamine vs guanfacine** | | | | | | | |
| Taylor, 2000 U.S. | Method not reported | Method not reported | Not reported | Yes | Yes but method not described | Not reported | Yes |
### Evidence Table 10. Quality Assessment of Head to Head Trials in Adults with ADHD

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Reporting of attrition, crossovers, adherence, and contamination</th>
<th>Loss to follow-up: differential / high</th>
<th>Intention-to-treat (ITT) analysis</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion SR vs methylphenidate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuperman, 2001</td>
<td>U.S.</td>
<td>Yes</td>
<td>No/ no</td>
<td>No: 81.1%</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Dextroamphetamine vs guanfacine** |
| Taylor, 2001  | U.S. | Yes | No/ no | Yes | No | Fair |
|                |        | NR | NR | NR |     |     |

| **Dextroamphetamine vs guanfacine** |
| Taylor, 2000  | U.S. | Yes | No/ no | No: 95.4% | No | Fair |
|                |        | NR | NR | NR |     |     |
### Evidence Table 10. Quality Assessment of Head to Head Trials in Adults with ADHD

**External Validity**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Number screened/ eligible/ enrolled</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion SR vs methylphenidate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kuperman, 2001 U.S.</td>
<td>NR/NR/37</td>
<td>Patients were excluded if they had a clinically significant chronic medical condition, another current Axis 1 diagnosis, a history of tic disorders, mental retardation (IQ &lt;80), organic brain disorders, clinically unstable psychiatric symptoms (suicidal behaviors, psychosis, violence, criminality), or substance abuse within 6 months; if taking other psychotropic medications. Any patient with a seizure history was excluded. Patients with eating disorders were excluded since they are predisposed to bupropion-induced seizures. Females of child-bearing potential were included only if using a medically approved form of contraception.</td>
<td></td>
</tr>
</tbody>
</table>

| **Dextroamphetamine vs guanfacine** | | | |
| Taylor, 2001 U.S. | NR/NR/17 | Excluded conditions already associated with frontostriatal pathology, including organic brain disorders, schizophrenia, and Tourette disorder; also excluded subjects with psychopathology possibly caused by neurologic insult. Also excluded medical conditions likely to affect mood or cognition, such as metabolic disorders, CNS conditions, mental retardation, untreated endocrine disorders, and pregnancy. Subjects using substances such as cannabis, amphetamines, cocaine, and heroin within 6 months of beginning drug trials were excluded. Subjects taking tricyclics, venlafaxine, or bupropion within 3 months, or stimulants within 2 weeks, before study were excluded. |

| **Dextroamphetamine vs guanfacine** | | | |
| Taylor, 2000 U.S. | 29/22/22 | Excluded narcolepsy and conditions associated with altered cognitive abilities including schizophrenia, Tourette's disorder, and diagnosable neurologic conditions; also excluded subjects with neurological soft signs that may be associated with frontal lobe cognitive deficits. Also excluded medical conditions likely to affect mood and condition, such as metabolic disorders, mental retardation, untreated endocrine disorders, and pregnancy. Also excluded the following: subjects using any cannabis, cocaine, heroin, or nonprescription amphetamines within 6 months of trial; subjects taking tricyclic antidepressants, venlafaxine, or bupropion within 3 months of trial; subjects taking prescription stimulants within 2 weeks prior to trial. |
## Evidence Table 10. Quality Assessment of Head to Head Trials in Adults with ADHD

**External Validity**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Run-in / Washout</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion SR vs methylphenidate</strong></td>
<td>Kuperman, 2001 U.S.</td>
<td>Lead-in yes; Washout NR</td>
<td>No</td>
<td>Yes</td>
<td>Glaxo Wellcome</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Dextroamphetamine vs guanfacine</strong></td>
<td>Taylor, 2001 U.S.</td>
<td>Run-in NR; 4-day washout between treatments</td>
<td>No</td>
<td>Yes</td>
<td>Not reported</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Dextroamphetamine vs guanfacine</strong></td>
<td>Taylor, 2000 U.S.</td>
<td>Run-in NR; 4-day washout between treatments</td>
<td>No</td>
<td>Yes</td>
<td>Not reported</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Run-in/ Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphetamine mixture</strong></td>
<td></td>
<td></td>
<td>Each medication was prescribed bid, taken at 7:30 AM and 2:30 PM.</td>
<td>Run-in NR; 1-week blinded placebo washout between phases</td>
<td>Not reported (NR)</td>
</tr>
<tr>
<td>Spencer,</td>
<td>2001</td>
<td>U.S. (Fair)</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michelson,</td>
<td>2003</td>
<td>31 outpatient sites in North America, country not otherwise specified (Fair)</td>
<td>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</td>
<td>1-week washout, followed by 2-week placebo lead-in phase</td>
<td>NR</td>
</tr>
<tr>
<td>Wernicke,</td>
<td>2004</td>
<td>U.S. (Fair)</td>
<td>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.</td>
<td></td>
<td>NR/NR</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>2001</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>HAM-D, HAM-A, BDI before and after each arm of the study. CGI and ADHD rating scale administered weekly. Neuropsychological test battery was administered 3 times, at baseline and after each study arm, and included an auditory version of the CPT, the Stroop test, and the Rey-Osterrieth Complex Figure. Improvement was defined as either a 30% reduction in the ADHD rating scale or &quot;much&quot; or &quot;very much improved&quot; on the CGI scale.</td>
<td>56% male</td>
<td>Mean age 38.8</td>
<td>96% white</td>
</tr>
<tr>
<td>Michelson</td>
<td>2003</td>
<td>31 outpatient sites in North America, country not otherwise specified</td>
<td>(Fair)</td>
<td>Self-rated version of CAARS and WRAADDS at baseline and endpoint; HAM-A and HAM-D; social and occupational functioning were assessed using the self-rated Sheehan Disability scale. Primary outcome: sum of the Inattention and Hyperactivity/Impulsivity subscales of the investigator-rated CAARS</td>
<td>Mean age 40.2</td>
<td>63.6% male</td>
<td>Ethnicity NR</td>
</tr>
<tr>
<td>Wernicke</td>
<td>2004</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Visits at weekly intervals assessed CAARS, HAM-D, HAM-A</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country (Quality Score)</td>
<td>Other population characteristics</td>
<td>Number screened/eligible/enrolled N per drug</td>
<td>Number withdrawn/lost to fu/analyzed: N per drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>-------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamine mixture</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spencer, 2001</td>
<td>U.S. (Fair)</td>
<td></td>
<td>93% had at least 1 lifetime comorbid psychiatric disorder</td>
<td>103/41/30</td>
<td>3 (10%) withdrawals; 0% lost to fu; 27 (90%) analyzed. N per drug not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michelson, 2003</td>
<td>31 outpatient sites in North America, country not otherwise specified (Fair)</td>
<td></td>
<td>67% had 1 or more first- or second-degree relatives with ADHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wernicke, 2004</td>
<td>U.S. (Fair)</td>
<td></td>
<td>93% had at least 1 lifetime comorbid psychiatric disorder</td>
<td>103/41/30</td>
<td>3 (10%) withdrawals; 0% lost to fu; 27 (90%) analyzed. N per drug not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atmooxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michelson, 2003</td>
<td>31 outpatient sites in North America, country not otherwise specified (Fair)</td>
<td>Study I / Study II, ADHD subtype: Combined 71.8% / 60.5% Inattention 27.5% / 35.1% Hyperactive/Impulsive 0.7% / 4.3%</td>
<td>448/329/280</td>
<td>71 (25%) withdrew; 22 (7.8%) lost to fu; 267 (95%) analyzed (atomoxetine n=133, placebo n=134)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wernicke, 2004</td>
<td>U.S. (Fair)</td>
<td>Not reported</td>
<td></td>
<td>NR/NR/380</td>
<td>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)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Final Report Drug Effectiveness Review Project

Pharmacologic Treatments for ADHD
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphetamine mixture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spencer, 2001</td>
<td>U.S.</td>
<td>Fair</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean change in ADHD rating scale during first treatment phase (Weeks 1-3), adderall vs placebo:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-12 vs +1 (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Michelson, 2003</td>
<td>31 outpatient sites in North America, country not otherwise specified</td>
<td>Fair</td>
<td>Mean change in score, data combined from 1st and 2nd drug phases, adderall vs placebo:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPT: number of hits +9 vs +7.8, number of omissions -7.9 vs -6.2; number late -1.39 vs -1.74</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% of patients who improved, ie, &gt;30% reduction on ADHD rating scale: 70.4% vs 7.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>% of patients who were &quot;much&quot; or &quot;very much&quot; improved on CGI scale: 66.7% vs 3.7%</td>
<td></td>
</tr>
<tr>
<td><strong>Atomoxetine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michelson, 2003</td>
<td>31 outpatient sites in North America, country not otherwise specified</td>
<td>Fair</td>
<td>Mean change in score, atomoxetine vs placebo, Study I // Study II:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAARS-INV total ADHD symptom score -9.5 vs -6.0 (p=0.005) // -10.5 vs -6.7 (p=0.002)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAARS-INV Inattentive -5.0 vs -3.1 (p=0.010) // -5.8 vs -3.5 (p=0.001)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAARS-INV Hyperactive/Impulsive -4.5 vs -2.9 (p=0.017) // -4.7 vs -3.2 (p=0.013)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAARS-Self total ADHD Symptom score -16.0 vs -9.3 (p=0.002) // -17.3 vs -11.6 (p=0.008)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAARS-Self Inattentive -15.9 vs -8.6 (p=0.001) // -12.5 vs -8.8 (p=0.025)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CGI-ADHD-S -0.8 vs -0.4 (p=0.010) // -0.9 vs -0.5 (p=0.002)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>WRAADDS -5.3 vs -2.9 (p=0.002) // -4.5 vs -2.8 (p=0.041)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HAM-D-17 -0.3 vs -0.6 (ns) // +0.2 vs -1.0 (p=0.013)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HAM-A -1.0 vs -1.2 (ns) // -0.7 vs -1.0 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sheehan Disability total -4.5 vs -2.9 (p=0.022) // -4.4 vs -4.0 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sheehan Disability work life -1.6 vs -1.0 (p=0.007) // -1.8 vs -1.2 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sheehan Disability family life -1.5 vs -1.0 (ns) // -1.4 vs -1.6 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sheehan Disability social life -1.3 vs -0.9 (ns) // -1.2 vs -1.2 (ns)</td>
<td></td>
</tr>
<tr>
<td>Wernicke, 2004</td>
<td>U.S.</td>
<td>Fair</td>
<td>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:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CAARS total score -11.2::5.1 vs -11.4::3.6 vs -7.0::2.7 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HAM-A -0.5::-0.5 vs -1.8::0.2 vs -1.5::0.0 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HAM-D 0.4::-0.5 vs -1.1::0.0 vs -0.9::0.4 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphetamine mixture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spencer, 2001</td>
<td>U.S. (Fair)</td>
<td></td>
<td>Elicited by investigator; HAM-D, HAM-A, BDI</td>
<td>Adderall vs placebo:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insomnia 37 vs 14.8% (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Loss of appetite 29.6 vs 11.1% (p=0.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anxiety 25.9 vs 14.8% (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Headache 11.1 vs 7.41% (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Agitation 22.2 vs 7.4% (p=0.05)</td>
</tr>
<tr>
<td><strong>Atomoxetine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michelson, 2003</td>
<td>31 outpatient sites in North America, country not otherwise specified (Fair)</td>
<td>Elicited by investigator</td>
<td>Atomoxetine vs placebo:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dry mouth 21.2 vs 6.8% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insomnia 20.8 vs 8.7% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nausea 12.3 vs 4.9% (p=0.003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased appetite 11.5 vs 3.4% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Constipation 10.8 vs 3.8% (p=0.002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Libido decreased 7.1 vs 1.9% (p=0.006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dizziness 6.3 vs 1.9% (p=0.015)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Difficulty attaining or maintaining erection (among males) 9.8 vs 1.2% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sweating 5.2 vs 0.8% (p=0.004)</td>
</tr>
<tr>
<td><strong>Wernicke, 2004</strong></td>
<td>U.S. (Fair)</td>
<td></td>
<td>Elicited by investigators, via open-ended questioning, and the Association for Methodology and Documentation in Psychiatry-5: Somatic Signs</td>
<td>% in atomoxetine-abrupt vs atomoxetine-tapered vs placebo:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Headache 4.4 vs 10.6 vs 4.1% (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain in limb 3.3 vs 1.1 vs 0% (p=0.019)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea 2.2 vs 5.3 vs 2.6% (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sinusitis 2.2 vs 4.3 vs 0.5 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insomnia 1.1 vs 5.3 vs 3.1 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Irritability 0 vs 4.3 vs 0% (p=0.007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dyspepsia 0 vs 4.3 vs 0.5% (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Allergic reactions: 1.1 vs 6.5 vs 1.5% (p=0.036)</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>By treatment, total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amphetamine mixture</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spencer, 2001</td>
<td></td>
<td>U.S. (Fair)</td>
<td>Adderall vs placebo:</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total withdrawals: 0 vs 3 (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Withdrawals due to AEs not reported</td>
<td></td>
</tr>
<tr>
<td><strong>Atomoxetine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michelson, 2003</td>
<td></td>
<td>31 outpatient sites in North America, country not otherwise specified (Fair)</td>
<td>Atomoxetine vs placebo:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total withdrawals: 73 (27%) vs 55 (20.7%), (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Withdrawals due to AEs:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23 (8.5%) vs 9 (3.4%), (p=0.03)</td>
<td></td>
</tr>
<tr>
<td>Wernicke, 2004</td>
<td></td>
<td>U.S. (Fair)</td>
<td>Atomoxetine-abrupt vs atomoxetine-taper vs placebo:</td>
<td>Depressive or anxiety symptoms did not significantly increase following drug discontinuation.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total withdrawals: 0 vs 1 (1%) vs 1 (0.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Withdrawals due to AEs:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (1%) in atomoxetine-taper discontinuation phase, due to headache</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Run-in/ Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>1998</td>
<td>U.S. (Fair)</td>
<td>Tomoxetine vs placebo.</td>
<td>Run-in NR/ 1 week of washout between the two 3 week periods.</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients randomized to Tomoxetine 40 mg/day in week 1, and 80 mg/day in weeks 2 and 3; or placebo.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilens</td>
<td>2001</td>
<td>U.S. (Fair)</td>
<td>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.</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weekly supplies of bupropion and placebo were dispensed in 100-mg capsules.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo mean dose at week 6: 379 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration 6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paterson</td>
<td>1999</td>
<td>Australia (Fair)</td>
<td>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</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Atmoxetine</th>
<th>Bupropion</th>
<th>Dexamphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improvement was defined as a reduction in ADHD Rating scale score of 30% or more. Following tests after each arm: ADHD Rating Scale (6) (weekly) Hamilton Depression Rating Scale Beck Depression Inventory Hamilton Anxiety Rating Scale Continuous Performance Test Stroop Tests Wisconsin Card Sorting Test Rey-Osterrieth Complex Figure</td>
<td>CGI Severity and Improvement scales, and the ADHD Rating Scale were administered at baseline and weekly visits. HAM-D, BDI, and HAM-A were administered at baseline and end of study. Categorical improvement was defined as a reduction in ADHD Rating Scale score of 30% or better.</td>
<td>DSM-IV ADHD criterion list with modified thresholds (see comments) were administered at baseline, 3 weeks, and 6 weeks. Patients’ relatives were also asked to fill out these questionnaires for comparison. Patients completed the BSI, a 53-item self-report symptom inventory, at baseline and weeks 3 and 6. Three CGI subscales were used at baseline and week 6: Severity at baseline, Improvement at 6 weeks, and an Efficacy Index was calculated by using a ratio of benefits against side effects. Patient satisfaction was measured at the end of the trial on a 5-point Likert Scale.</td>
</tr>
<tr>
<td>Spencer,</td>
<td>1998</td>
<td>U.S. (Fair)</td>
<td>n=21</td>
<td>Mean age 38.3</td>
<td>Mean age 35.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55% male</td>
<td>60% male</td>
</tr>
<tr>
<td>Wilens,</td>
<td>2001</td>
<td>U.S. (Fair)</td>
<td></td>
<td>Ethnicity NR</td>
<td>Ethnicity NR</td>
</tr>
<tr>
<td>Paterson,</td>
<td>1999</td>
<td>Australia (Fair)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>Other population characteristics</th>
<th>Number screened/eligible</th>
<th>Number withdrawn/lost to fu/analyzed</th>
<th>Number per drug</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atmoxetine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spencer,</td>
<td>1998</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>1 lifetime comorbid psychiatric disorder (n=13)</td>
<td>screened NR</td>
<td>1 withdrawn/ 0 lost to fu</td>
<td>n=11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>current ratings of severe depression or anxiety (n=2)</td>
<td>22 enrolled</td>
<td>21 analyzed</td>
<td>Placebo: n=10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>family history of ADHD (n=20)</td>
<td>Tomoxetine: n=11</td>
<td>Tomoxetine: n=11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>average to above-average intelligence (n=21).</td>
<td>Placebo: n=10</td>
<td>Placebo: n=10</td>
<td></td>
</tr>
<tr>
<td><strong>Bupropion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilens,</td>
<td>2001</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Inattentive subtype 58%</td>
<td>154/NR/40</td>
<td>2 (5%) withdrawn; 0% lost to fu; 40 (100%) analyzed: Bupropion n=21, Placebo n=19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Combined subtype 35%</td>
<td>Bupropion n=21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperactive or impulsive subtypes 8%</td>
<td>Placebo n=19</td>
<td>40 (100%) analyzed: Bupropion n=21, Placebo n=19</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Major depression: past 59%, current 19%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Two or more anxiety disorders: past 19%, current 8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Substance abuse/dependence: past 35%, current 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Smoking: past 33%, current 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alcohol abuse/dependence: past 33%, current 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antisocial personality disorder: past 16%, current 0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dexamphetamine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paterson,</td>
<td>1999</td>
<td>Australia</td>
<td>(Fair)</td>
<td>51% were inattentive type</td>
<td>68/51/45</td>
<td>1 (2.2%) withdrawn</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>46.7% were combined inattentive and hyperactive types</td>
<td>24 dexamphetamine</td>
<td>0% lost to follow up</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2% were hyperactive type</td>
<td>21 placebo</td>
<td>45 (100%) analyzed: Dexamphetamine n=24, Placebo n=21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atmoxetine</td>
<td></td>
<td></td>
<td><strong>Results</strong></td>
</tr>
<tr>
<td>Spencer,</td>
<td>1998</td>
<td>U.S. (Fair)</td>
<td>Decrease in ADHD symptoms:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>tomoxtetine: (11/21 subjects)-- week 2: p&lt; 0.01; week 3: p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo: (2/10 subjects).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(3 week study)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Results from scales and tests at end of study</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>reported as: paired tests of tomoxtetine scores vs placebo scores; p-value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>McNemar test: (x= 7.4, df=1; p&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroop Color Word test: (z=2.6, n=21, p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interference T test scores: (z=2, n=21, p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADHD rating scale: p-value= ns</td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
<td></td>
<td><strong>Bupropion vs placebo:</strong></td>
</tr>
<tr>
<td>Wilens,</td>
<td>2001</td>
<td>U.S. (Fair)</td>
<td>CGI improvement rating of 1 (much improved) or 2 (very much improved): 52 vs 11%, p=0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improved by 30% or more reduction in DSM-IV ADHD symptom checklist score: 76 vs 37% (p=0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean change from baseline to 6 weeks in ADHD symptom checklist score: -42% vs -24% (p=0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Proportion of the 18 DSM-IV ADHD-specific symptoms that improved: 100 vs 44% (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Depression and anxiety (HAM-D, BDI, HAM-A): no difference between groups</td>
</tr>
<tr>
<td>Dexamphetamine</td>
<td></td>
<td></td>
<td><strong>Dexamphetamine vs placebo:</strong></td>
</tr>
<tr>
<td>Paterson,</td>
<td>1999</td>
<td>Australia (Fair)</td>
<td>Mean change in score from 0 to 6 weeks, p-values signifying change from baseline, dexamphetamine vs placebo:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADHD score, Hyperactive -2.0 (p=0.004) vs -1.0; Inattentive -3.83 vs -1.57 (ns); Total -5.83 (p&lt;0.0001) vs -3.57 (p=0.042)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BSI mean T-score, Anxiety -8.2 (p&lt;0.001) vs -5.43 (p&lt;0.001); Depression -3.59 (ns) vs -2.76 (ns); Global Severity Index -5.5 (ns) vs -6.19 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Efficacy Index at week 6:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% of placebo had equal levels of benefits and side-effects; 75% of dexamphetamine had greater benefits than side-effects (p&lt;0.001)</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atmoxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spencer,</td>
<td>1998</td>
<td>U.S. (Fair)</td>
<td>self-report from patients</td>
<td>no serious adverse events observed, 1 subject withdrawn after becoming ery anxious on tomoxetine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilens,</td>
<td>2001</td>
<td>U.S. (Fair)</td>
<td>Elicited by investigator at each visit</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paterson,</td>
<td>1999</td>
<td>Australia (Fair)</td>
<td>Weight loss and evaluation of blood pressure were assessed at weeks 3 and 6. Urinalysis was conducted at baseline and weeks 6 to ensure compliance and exclude drug abuse. Patients kept a diary of side effects.</td>
<td>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&lt;0.001) vs -0.286 kg (ns)</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>By treatment, total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atmoxetine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spencer, 1998 U.S. (Fair)</td>
<td></td>
<td>1/21 (due to increased anxiety in patient)</td>
<td>3 week study period.</td>
<td></td>
</tr>
<tr>
<td>placebo: 0 withdrawals;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bupropion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilens, 2001 U.S. (Fair)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion vs placebo,</td>
<td></td>
<td>Total withdrawals:</td>
<td>Due to AEs: 0 vs 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (9.52%, noncompliance) vs 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dexamphetamine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paterson, 1999 Australia (Fair)</td>
<td></td>
<td>Dexamphetamine vs placebo,</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total withdrawals:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (4.2%) vs 0%</td>
<td>Due to AEs:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (4.2%, depression) vs 0%</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country (Quality Score)</td>
<td>Interventions (drug, regimen, duration)</td>
<td>Run-in/ Washout Period</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>-------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bouffard,</td>
<td>2003</td>
<td>Canada (Fair)</td>
<td>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).</td>
<td>3-day run-in of increasing dosages (15/30/45 mg/day); 5 to 7-day washout btw. active &amp; placebo phases</td>
</tr>
<tr>
<td>Cox,</td>
<td>2000</td>
<td>U.S. (Fair)</td>
<td>Methylphenidate 10 mg/day, single dose Placebo (vitamin C), single dose</td>
<td>NR/NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouffard</td>
<td>2003</td>
<td>Canada</td>
<td>(Fair)</td>
<td>2 self-rating questionnaires (CAARS &amp; AAPBS); SCL-90, BDI, HAM-A; GAF</td>
<td>Mean age 34</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity NR</td>
</tr>
<tr>
<td>Cox</td>
<td>2000</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>The Atari Research Driving Simulator had 2 equivalent driving courses with similar driving demands. The 16-mile</td>
<td>Mean age 22.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>courses take approximately 30 minutes to complete when following posted speed limits. The simulator quantifies</td>
<td>100% male</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>steering, braking, and crash variables.</td>
<td>77% white</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>After completing the simulation, subjects were asked to rate their driving performance on a 5-point scale (1=poor,</td>
<td>15% black</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5=well).</td>
<td>7.7% Asian</td>
</tr>
</tbody>
</table>
# Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>Other population characteristics</th>
<th>Number screened/ eligible/ enrolled N per drug</th>
<th>Number withdrawn/ lost to fu/ analyzed: N per drug</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methylphenidate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bouffard,</td>
<td>2003</td>
<td>Canada</td>
<td>(Fair)</td>
<td>Mean IQ 101</td>
<td>93/NR/38</td>
<td>8 (21%) withdrawn</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Same subjects exposed to both treatments</td>
<td></td>
<td>Loss to followup NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30 (79%) analyzed, same subjects exposed to both treatments (phases were combined in analysis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADHD patients vs non-ADHD controls:</td>
<td>NR/NR/13</td>
<td>0% withdrawn;</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Mean # motor vehicle violations, 2.6 vs 1.5 (p=0.06)</td>
<td></td>
<td>0% loss to followup:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean # automobile crashes, 2.7 vs 0.8 (p=0.018)</td>
<td></td>
<td>13 (100%) analyzed, same subjects exposed to both treatments (phases were combined in analysis)</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouffard,</td>
<td>2003</td>
<td>Canada</td>
<td>Fair</td>
<td>Mean change in condition from baseline, methylphenidate 30 mg/day vs methylphenidate 45 mg/day vs placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(p-values compare placebo with methylphenidate):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adult behavior problems -1 vs -1 -0.7 (p&lt;0.005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CAARS -0.8 vs -0.9 vs -0.5 (p&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CPT% commission error -17.1 vs -19.4 vs -9.8 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CPT% omission error -3.3 vs -3.0 vs -0.5 (p&lt;0.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stop-signal task vs -35.8 vs -47 vs -29.05 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HAM-R -0.4 vs -0.5 vs -0.35 (p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BDI -5.5 vs -5.5 vs -4.4 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SCL-90-R -9.8 vs -11 vs -7.45 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Obsessive-compulsive scale -12 vs -13 vs -7.5 (p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hostility scale -6.0 vs -6.8 vs -3.5 (ns)</td>
</tr>
<tr>
<td>Cox,</td>
<td>2000</td>
<td>U.S.</td>
<td>Fair</td>
<td>Placebo vs ritalin, mean Impaired Driving Score (score of 0 would be average, +1 would be one standard deviation worse than the mean):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADHD patients +0.5 vs +2.4 (p=0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-ADHD controls +0.6 vs -1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean self-rated driving performance, ADHD patients vs non-ADHD controls:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 3.0 vs 3.9 (p=0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ritalin: 3.5 (+0.5 better than placebo) vs 3.6 (-0.3 worse than placebo), (ns)</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouffard,</td>
<td>2003</td>
<td>Canada</td>
<td>Fair</td>
<td>Self-rated</td>
<td>Change from baseline in % of subjects reporting condition, methylphenidate 45 mg/day vs placebo:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild appetite loss +23 vs +5% (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild trouble sleeping -2 vs -7% (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate trouble sleeping -13 vs -9% (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild headache -4 vs +5% (ns)</td>
</tr>
<tr>
<td>Cox,</td>
<td>2000</td>
<td>U.S.</td>
<td>Fair</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>By treatment, total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouffard,</td>
<td>2003</td>
<td>Canada</td>
<td>Fair</td>
<td>Methylphenidate vs placebo, Total withdrawals unclear by treatment group; 4 enrolled withdrew on methylphenidate <em>because they were not blind</em> to treatment. Withdrawals due to AEs (n=1, 2.6%), treatment group unclear.</td>
<td>Data from the first treatment phase was not reported separately. Concealment of allocation is a concern: &quot;Not blind to methylphenidate,&quot; 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).</td>
</tr>
<tr>
<td>Cox,</td>
<td>2000</td>
<td>U.S.</td>
<td>Fair</td>
<td>Methylphenidate vs placebo, Total withdrawals: 0 vs 0 Withdrawals due to AEs: 0 vs 0</td>
<td>Data from the first treatment phase was not reported separately. Author concludes that Ritalin improved ADHD driving performance to the non-ADHD level.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country (Quality Score)</td>
<td>Interventions (drug, regimen, duration)</td>
<td>Run-in/ Washout Period</td>
<td>Allowed other medications/ interventions</td>
</tr>
<tr>
<td>---------------------</td>
<td>--------</td>
<td>-------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Gualtieri, 1985 U.S. (Fair)</td>
<td></td>
<td>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.</td>
<td>Run-in NR; 68-hr washout between treatment phases</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country (Quality Score)</td>
<td>Method of Outcome Assessment and Timing of Assessment</td>
<td>Age</td>
<td>Gender</td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>-------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>Gualtieri,</td>
<td>1985</td>
<td>U.S. (Fair)</td>
<td>On the first day of each treatment phase, a nurse measured pulse and blood pressure in seated subjects, and a blood sample was drawn to measure baseline growth hormone (GH) levels. 1 hour after the first dose of MPH or placebo, pulse and blood pressure were again measured, followed by a second blood sample for MPH serum levels and GH. Subjects then completed the CPT with a wristwatch actometer on the nondominant arm. At the end of each treatment phase, subjects filled out the AAS, ZSDS, and ZSAS and reported their subjective experiences. Before the drug code was broken, subjects were asked to guess which drug was MPH and which was placebo.</td>
<td>Mean age 27.2</td>
<td>100% male</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Other population characteristics</th>
<th>Number screened/ enrolled</th>
<th>Number withdrawn/ lost to fu/ analyzed:</th>
<th>N per drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gualtieri,</td>
<td>1985</td>
<td>U.S.</td>
<td>Fair</td>
<td>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.</td>
<td>NR/NR/8</td>
<td>NR/NR/8</td>
<td>N per drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Same subjects exposed to both treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Placebo</th>
<th>MPH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gualtieri,</td>
<td>1985</td>
<td>U.S. (Fair)</td>
<td>27.7</td>
<td>25.8</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45.3</td>
<td>37.5</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>38.3</td>
<td>33.8</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>121.8</td>
<td>128.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.3</td>
<td>2.1</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>98.6</td>
<td>60.3</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.3</td>
<td>6.0</td>
<td>ns</td>
</tr>
</tbody>
</table>

MPH significantly improved correct responses on the CPT.
All subjects accurately guessed the active drug condition.
**Evidence Table 11. Placebo-controlled trials in adults with ADHD**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gualtieri,</td>
<td>1985</td>
<td>U.S.</td>
<td>Fair</td>
<td>NR</td>
<td>AEs were not reported among the 8 subjects who participated in the short-term DB RCT.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Quality Score</td>
<td>By treatment, total withdrawals; withdrawals due to adverse events</td>
<td>Comments</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>---------------</td>
<td>---------------------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Gualtieri, 1985</td>
<td>U.S.</td>
<td>Fair</td>
<td></td>
<td>Methylphenidate vs placebo, Total withdrawals 0 vs 0, Withdrawals due to AEs 0 vs 0</td>
<td>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.</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Run-in/Washout Period</th>
<th>Allowed other medications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td></td>
<td>Kinsbourne, 2001 U.S. (Fair)</td>
<td>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</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levin 2002 U.S. (Fair)</td>
<td>Placebo Nicotine transdermal patches: Week 1=5 mg per day, Weeks 2-3=10 mg per day Nicotine+methylphenidate sustained release</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Methylphenidate sustained release 20 mg per day Nicotine+methylphenidate sustained release</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Duration: 4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Quality Score</td>
<td>Method of Outcome Assessment and Timing of Assessment</td>
<td>Age</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>---------</td>
<td>---------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Kinsbourne</td>
<td>2001</td>
<td>U.S.</td>
<td>Fair</td>
<td>CPALT - 30-minute test, 4 sessions. On each day of assessment, patient was tested at time zero (baseline), 2 hours after drug administration, in a randomized sequence, counterbalanced across subjects. Favorable response was defined as performance on one of the drug conditions 25% or more above that on placebo. Adverse response was 25% below placebo. Outcomes between those extremes was recorded as non-response.</td>
<td>Mean age=34</td>
</tr>
<tr>
<td>Levin</td>
<td>2002</td>
<td>U.S.</td>
<td>Fair</td>
<td>CGI scale assessed by clinician on Treatment Days 1, 8 and 21. Individual questions from the Profile of Mood States (POMS) battery (tension, fatigue, vigor, depression, anger and difficulty concentrating: Treatment days 1, 8, 15 and 21. Conners CPT: Treatment days 1 and 21. Automated Neuropsychological Assessment Metrics (ANAM): simple reaction time, mental spatial rotation reaction time and delayed matching to sample administered on Treatment Days 1 and 21.</td>
<td>Mean age=37</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>Other population characteristics</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed: N per drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinsbourne,</td>
<td>2001</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>None of the subjects had been previously diagnosed with ADHD, and none were currently taking psychoactive drugs.</td>
<td>NR/NR/17</td>
<td>0% withdrawn</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Same subjects exposed to all treatments</td>
<td></td>
<td>0% lost to followup</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17 (100%) analyzed; N per drug not reported (phases were combined in analysis)</td>
</tr>
<tr>
<td>Levin</td>
<td>2002</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>NR</td>
<td>NR/NR/40</td>
<td>6 (15%) withdrawn/lost to fu nr/34 analyzed (placebo n=7, nicotine n=9, MPH n=9, combination n=9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo patch + placebo pill, n=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nicotine, n=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methylphenidate, n=10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nicotine + methylphenidate, n=10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinsbourne,</td>
<td>2001</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>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</td>
</tr>
</tbody>
</table>

### Methylphenidate

- **Levin, 2002**  
  - **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
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinsbourne,</td>
<td>2001</td>
<td>U.S.</td>
<td>Fair</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Levin</td>
<td>2002</td>
<td>U.S.</td>
<td>Fair</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>By treatment, total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinsbourne, Methylphenidate</td>
<td>2001</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Methylphenidate (5/10/20 mg/day) vs placebo, total withdrawals: 0/0/0 vs 0, withdrawals due to AEs: 0/0/0 vs 0</td>
<td>Data from the first treatment phase was not reported separately.</td>
</tr>
<tr>
<td>Levin Methylphenidate</td>
<td>2002</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Methylphenidate vs placebo, total withdrawals: 1 (10%) vs 3 (30%); p=NS, withdrawals due to adverse events nr</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Run-in/ Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattes, 1984</td>
<td>U.S.</td>
<td>Fair</td>
<td>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. Methylenphidate 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.</td>
<td>NR/NR</td>
<td>NR; drug or alcohol abuse was allowed</td>
</tr>
<tr>
<td>Schubiner, 2002</td>
<td>U.S.</td>
<td>Fair</td>
<td>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.</td>
<td>NR/NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattes,</td>
<td>1984</td>
<td>U.S.</td>
<td>To determined childhood history of ADHD, patients completed questionnaires including items from CTQ; if a parent was accessible, the parent was asked to quantitate the patient's childhood behavior (CPQ); a relative was asked to complete a modified version of the adult ADD questionnaire; and school records were requested. Patient and psychiatrist rated global improvement weekly; self-rated adult ADD questionnaire, SCL-90, POMS completed at weeks 3 and 6. A study psychiatrist completed a structured interview form of 23 ratings of adult ADD symptoms.</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Schubiner,</td>
<td>2002</td>
<td>U.S.</td>
<td>ADHD outcome measures (administered at weeks 5, 9 and 13) ADHD Symptom Checklist Global Improvement Scale Beck Depression Inventory Substance use outcomes Urinalysis Addiction Severity Index (ASI) - every visit Tiffany Cocaine Craving Scale - monthly Self-report - beginning of each study week</td>
<td>Mean age=37.5</td>
<td>89.6% male</td>
<td>70.8% white</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed: N per drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattes, 1984</td>
<td></td>
<td>U.S. (Fair)</td>
<td>29 patients with childhood ADHD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>37 patients without childhood ADHD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DSM-III diagnoses of subjects:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADD residual type 42.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antisocial personality disorder 7.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alcoholism 10.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug abuse 24.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Borderline personality disorder 24.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Major depressive episode (mild) 28.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Generalized anxiety disorder 10.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other 68.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2829/116/66</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Same subjects exposed to both treatments</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 (7.6%) withdrawn; Loss to followup NR; 61 (92.4%) analyzed; N per drug not reported (phases were combined in analysis).</td>
<td></td>
</tr>
</tbody>
</table>

**Methylphenidate**

<table>
<thead>
<tr>
<th>Schubiner, 2002</th>
<th>U.S. (Fair)</th>
<th>No. days using cocaine in last 30 days=13.52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. hyperactive symptoms=5.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. inattentive symptoms=4.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean BDI scores=22.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug use=0.2242</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alcohol use=0.1605</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Illegal activity=0.1172</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medical condition=0.1080</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Family relations=0.3047</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychiatric status=0.3324</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Employment=0.4503</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Affective disorders=56%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety disorders=12.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other Axis I disorders=4.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>932/338/59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylphenidate n=24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo n=24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemoline n=11 (dropped from analysis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MPH n=24, placebo n=24</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattes,</td>
<td>1984</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>No response to methylphenidate occurred in either patients with or without childhood ADHD. Results among patients without childhood ADHD were not shown.</td>
</tr>
</tbody>
</table>
| Schubiner,  | 2002 | U.S.    | (Fair)        | 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)  
MPH vs placebo (mean change); differences NS unless otherwise specified  
No. inattentive symptoms=2.13 (-2.79) vs 2.83 (-1.96)  
No. hyperactive symptoms=3.42 (-2) vs 4.78 (-1.47)  
No. days using cocaine in past 30 days=15.42 (+2.13) vs 14.58 (+0.83)  
Amount spent on cocaine in past 30 days=$62.54 vs $97.19  
Longest continuous abstinence=5.17 vs 5.17  
% Urine samples tested negative for cocaine=0.5 vs 0.42  
Physician efficacy ratings showing moderate improvement: 77% vs 21%, p<0.05  
at 4 weeks: 77% vs 44%  
at 8 weeks: 60% vs 36%  
at 12 weeks: 50% vs 56%  
last visit: 73% vs 42%, p<0.05  
Mean participant efficacy ratings at last visit: 1.88 vs 2.68; p<0.05  
at 4 weeks: 2.57 vs 3.00  
at 8 weeks: 2.08 vs 3.08  
at 12 weeks: 1.75 vs 2.64 |
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattes,</td>
<td>1984</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>SADS-C elicited by investigator</td>
<td>The following AEs occurred significantly ($p&lt;0.05$) with methylphenidate: more anorexia, headaches, late-afternoon depression, and less psychiatrist-rated impulsivity. Numeric results for AEs were not shown.</td>
</tr>
<tr>
<td>Schubiner,</td>
<td>2002</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Side effects checklist based on Barkley's (1990) version with the addition of cardiac symptoms</td>
<td>MPH vs placebo (<em>differences NS unless otherwise specified</em>) (% worst occurrence during study)</td>
</tr>
</tbody>
</table>

- **Chest pain**: $0$ vs $2$ (8%)
- **Palpitations**: $0$ vs $1$ (4%)
- **Dizzy**: $2$ (8%) vs $1$ (4%)
- **Stomachaches**: $3$ (13%) vs $3$ (13%)
- **Nightmares**: $5$ (21%) vs $3$ (13%)
- **Headaches**: $6$ (25%) vs $6$ (25%)
- **Nausea or upset stomach**: $8$ (33%) vs $5$ (21%)
- **Euphoria, unusually happy**: $10$ (42%) vs $7$ (29%)
- **Drowsiness**: $6$ (25%) vs $10$ (42%)
- **Tics or nervous movement**: $5$ (17%) vs $5$ (21%)
- **Decreased appetite**: $12$ (50%) vs $6$ (25%)
- **Insomnia or trouble sleeping**: $15$ (63%) vs $8$ (33%); $p<0.05$
- **Irritability**: $14$ (58%) vs $13$ (54%)
- **Sadness**: $15$ (63%) vs $9$ (38%)
- **Talk less with others**: $11$ (46%) vs $12$ (50%)
- **Stare a lot or daydream**: $12$ (50%) vs $17$ (71%)
- **Anxious**: $19$ (79%) vs $15$ (63%)
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>By treatment, total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattes, 1984</td>
<td>U.S.</td>
<td>(Fair)</td>
<td></td>
<td>Methylphenidate vs placebo: Total withdrawals unclear by treatment group; Withdrawals due to AEs not reported.</td>
<td>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.</td>
</tr>
<tr>
<td>Schubiner, 2002</td>
<td>U.S.</td>
<td>(Fair)</td>
<td></td>
<td>Methylphenidate vs placebo: Total withdrawals: 13 (54.2%) vs 10 (41.7%) Withdrawals due to adverse events: 0 vs 1 (4.2%)</td>
<td>Comorbid for cocaine dependence Pemoline arm dropped (n=11) due to low enrollment after 1 year</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Run-in/ Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>1995</td>
<td>U.S.</td>
<td>Fair</td>
<td>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.</td>
<td>Run-in NR; 1-week washout between phases</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>U.S.</td>
<td>Poor</td>
<td>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.</td>
<td>NR/NR</td>
<td>Other psychoactive medications were not permitted</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>1995</td>
<td>U.S. (Fair)</td>
<td>Improvement defined as CGI score less than 2 and a reduction of at least 30% in individual rating scale scores. HAM-D, HAM-A, BDI before and after each arm of the study. CGI and ADHD rating scale administered weekly.</td>
<td>Mean age 40 43.5% male 100% white non-Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spencer</td>
<td>2005</td>
<td>U.S. (Poor)</td>
<td>Primary outcome: Adult ADHD Investigator System Report Scale (AISRS) and Clinical Global Impression (CGI) Scale. Responder status was defined as a 30% reduction in the AISRS plus &quot;much&quot; or &quot;very much improved&quot; in the CGI. Timing: weekly. Secondary outcome: Hamilton Depression Scale; Beck Depression Inventory; Hamilton Anxiety Scale. Timing: at the begining and end of the study</td>
<td>Mean age 37 58.2% male Ethnicity: NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Other population characteristics</th>
<th>Number screened/ eligible/enrolled N per drug</th>
<th>Number withdrawn/ lost to fu/ analyzed: N per drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>1995</td>
<td>U.S. (Fair)</td>
<td>74% had at least one past comorbid psychiatric disorder</td>
<td>85/25/25</td>
<td>2 (8%) withdrawn 0% lost to followup 23 (92%) analyzed. N per drug in 1st treatment phase not reported.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>56% had a current comorbid psychiatric disorder</td>
<td>N per drug during first phase not reported.</td>
<td></td>
</tr>
<tr>
<td>Spencer</td>
<td>2005</td>
<td>U.S. (Poor)</td>
<td>38% major depression 9% multiple (&gt;2) anxiety disorders</td>
<td>289/NR/146</td>
<td>36/NR/110</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>104 in MPH; 42 in placebo</td>
<td>26(25%) in MPH; 10(24%) in placebo dropout</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer,</td>
<td>1995</td>
<td>U.S.</td>
<td>Fair</td>
<td>Mean change in score during first treatment phase (Weeks 1-3), methylphenidate vs placebo:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ADHD Rating Scale -18 vs -2.5 (p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Global Severity subscale of the CGI Scale -1.8 vs 0 (p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean change in ADHD symptom cluster score, using 1st and 2nd treatment phases combined, methylphenidate vs placebo:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hyperactivity overall -1.2 vs -0.16 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Impulsivity overall -1.3 vs -0.44 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Inattentiveness -0.62 vs -0.26 (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>% of patients who improved, ie. CGI score &lt;2 and reduction &gt;=30% in individual rating score: 78% vs 4% (p&lt;0.001)</td>
</tr>
<tr>
<td>Spencer,</td>
<td>2005</td>
<td>U.S.</td>
<td>Poor</td>
<td>Methylphenidate vs placebo,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CGI rated &quot;much&quot; or &quot;very much&quot; improved: 63(68%) vs 6(17%), p&lt;0.001</td>
</tr>
</tbody>
</table>
Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer</td>
<td>1995</td>
<td>U.S.</td>
<td>Elicited by investigator; HAM-D, HAM-A, BDI</td>
<td>Loss of appetite 26%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td></td>
<td>Insomnia 22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anxiety 22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methylphenidate vs placebo: Mean heart rate 80 vs 76 beats/min (p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean weight 73.2 vs 74.3 kg (p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>self-report</td>
<td>Methylphenidate vs placebo, Life events: 2(2%) vs 0(0%), p=0.37</td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>U.S.</td>
<td></td>
<td>Psychiatric adverse events: 7(7%) vs 0(0%), p=0.085</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Poor)</td>
<td></td>
<td>Somatic complaints: 2(2%) vs 0(0%), p=0.37</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>By treatment, total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer,</td>
<td>1995</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>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%</td>
<td>Outcomes from the first phase of treatment (MPH vs placebo) are presented separately, but number of patients in each group is not reported.</td>
</tr>
<tr>
<td>Spencer,</td>
<td>2005</td>
<td>U.S.</td>
<td>(Poor)</td>
<td>Methylphenidate vs placebo, Total withdrawals 26 (25%) vs 10(24%); Withdrawals due to AEs: 11(11%) vs 0(0%)</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Run-in/ Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenenbaum, 2002</td>
<td>U.S.</td>
<td>Fair</td>
<td></td>
<td>All study medications were administered qid, 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</td>
<td>Run-in NR; 1-week washout between treatment phases</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenenbaum,</td>
<td>2002</td>
<td>U.S. (Fair)</td>
<td>Self-report rating scales, rating scales completed by the individual's significant other, and a computerized continuous performance test, conducted at baseline and end of each 3-week treatment phase, as well as 1 month after the final treatment condition.</td>
<td>Mean age 42</td>
<td>45.8% male</td>
<td>100% white</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td></td>
<td></td>
<td>Self-reported rating scales: Barkley's ADHD rating scale, Attention Deficit Scales for Adults, Copeland Symptom Checklist for Adult Attention Deficit Disorders, Barratt Impulsiveness Scale, Conners' CPT, Brown ADD scales Other-reported data: Barkley's ADHD Scale, Attention Deficit Scales for Adults, Copeland Symptom Checklist for Adult ADD, Brown ADD Scales</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Composite scores for each scale were calculated as follows: the mean baseline score was subtracted from each subject's score at the end of each 3-week treatment phase, divided by standard deviation at baseline for the entire sample. For each research instrument the standardized scores for the subscales were then summed to provide one composite score for each participant for each treatment condition.
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed: N per drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenenbaum,</td>
<td>2002</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>128/85/33</td>
<td>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).</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Not reported</td>
<td></td>
<td>Same subjects exposed to all treatments.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenenbaum,</td>
<td>2002</td>
<td>U.S. (Fair)</td>
<td><strong>Methylphenidate</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Composite score effect size; self-reported data; other-reported data:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Barkley’s ADHD Rating Scale  0.18/ 0.13; Attention Deficit Scales for Adults 0.19/0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Copeland Checklist for Adult ADD 0.20/0.23; Barratt Impulsiveness Scale 0.25/other na</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conners’ CPT 0.13/other na; Brown ADD Scales 0.25/0.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Mean change from baseline in MPH vs placebo [Cohen’s d effect size] from self-reported data; from other-reported data:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Barkley’s Inattention -2.75 v -2.79 [-.02] v -1.18 v -1.57 [-.15]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Barkley’s hyperactivity -1.79 v -1.79 [0.00] v -1.96 v -1.35 [-.17]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADS Attention-Focus -7.10 v -4.80 [-.33] v -2.50 v -3.50 [-.16]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADS Behavior-Disorganized Activity -9.00 v -7.80 [.13] v -6.60 v -5.80 [.08]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ADS Emotive Scale -4.90 v -5.10 [-.04] v -3.50 v -3.00 [.07]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Copeland Inattention/Distractibility -15.10 v -9.40 [.30] v -1.90 v -8.20 [-.40]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Copeland Impulsivity Scale -15.00 v -11.20 [.21] v -5.10 v -7.80 [-.12]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Copeland Overactivity/Hyperactivity -8.40 v -16.50 [.42] v -3.60 v -7.90 [-.20]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Copeland Underactivity -12.50 v -8.20 [.22] v -4.80 v -5.20 [-.03]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Barratt Total scale -5.60 v -6.00 [-.04] v Other-reported data n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Barratt Cognitive impulsiveness scale -1.70 v -1.40 [.10] v Other-reported data n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Barratt motor impulsiveness -3.00 v -2.70 [.07] v Other-reported data n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Barratt non-planning impulsivity -9.0 v -2.00 [-.22] v Other-reported data n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPT: Standard Error of Hit Rate -1.27 v -1.25 [.01] v Other-reported data n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPT: SE of variability in reaction times -.30 v -1.89 [-.40] v Other-reported data n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPT: Hit rate minus interstimulus interv -.01 v -.01 [.10] v Other-reported data n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CPT: Intertrial interv -.01 v -.01 [-.02] v Other-reported data n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brown total score -15.60 v -15.10 [.02] v -12.80 v -18.80 [-.35]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brown: Activating and organizing to work -3.60 v -3.30 [.05] v -3.80 v -3.80 [-.15]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brown: Sustaining attention and concentr -3.90 v -3.30 [.13] v -2.70 v -4.70 [-.34]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brown: Sustaining effort and energy -3.60 v -3.20 [.07] v -2.70 v -3.80 [-.21]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brown: Managing affective interference -2.13 v -2.67 [-.14] v -1.80 v -2.30 [-.13]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Brown: Utilizing working memory and reca -2.30 v -2.70 [-.09] v -2.00 v -3.30 [.41]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Beck Depression -1.68 v -3.68 [-.31] v Other-reported data n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Beck Anxiety .12 v -2.17 [-.54] v Other-reported data n/a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Avg. effect size</strong> [-.02] v [-.18]</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenenbaum, 2002</td>
<td>U.S. (Fair)</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>By treatment, total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenenbaum, etc.</td>
<td>2002</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Methylphenidate vs placebo: Total withdrawals unclear by treatment group. Withdrawals due to AEs 0 vs 0</td>
<td>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.</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Run-in/ Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood,</td>
<td>1976</td>
<td>U.S.</td>
<td>Fair</td>
<td>Methyphenidate for 2 weeks twice daily, at variable, NR dose amounts, gradually increased to max of 60mg. Crossover: to methyphenidate, doses varying to 20-60 mg/day (specifics NR) of: Methylphenidate or Pemoline</td>
<td>Run-in NR. No washout given due to short duration of drug</td>
<td>Imipramine, 10mg, was used with 1 subject, who did not respond to Pemoline,</td>
</tr>
<tr>
<td>Turner,</td>
<td>2004</td>
<td>U.K.</td>
<td>Fair</td>
<td>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</td>
<td>Run-in NR; 1-week washout between single-dose treatment phases</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood,</td>
<td>1976</td>
<td>U.K. (Fair)</td>
<td>12 month assessment self-report of symptoms from patients, completion of self-report questionnaire</td>
<td>N=15</td>
<td>only 11 in</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cross-over</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Age Range: 21-60</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ethnicity: Caucasian</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male: 40% (of the 15 total)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Modafinil**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner,</td>
<td>2004</td>
<td>U.K. (Fair)</td>
<td>Patients were tested 2 hours post drug administration for approximately 2 hours. Testing sessions were</td>
<td>Mean age 28</td>
<td>65% male</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>separated by at least a week.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neuropsychological test battery, including CANTAB; Logan stop-signal task; PRM task; IDED; NTOL The order in which patients received the tasks differed for placebo and drug conditions and was randomized across patients.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Other population characteristics</th>
<th>Number screened/eligible/enrolled N per drug</th>
<th>Number withdrawn/lost to fu/analyzed: N per drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood,</td>
<td>1976</td>
<td>U.K. (Fair)</td>
<td></td>
<td>15/11 N per drug NR</td>
<td>0/0/11 analyzed: N NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RDC diagnoses:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>generalized anxiety disorder: n=8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cyclothymic disorder: n=4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>drug/alcohol abuse: n=2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>antisocial disorder: n=2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>minor depressive disorder: n=4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N&gt;15, as patients as patients over-lapped in these diagnoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turner,</td>
<td>2004</td>
<td>U.K. (Fair)</td>
<td>Mean NART score 108</td>
<td>NR/NR/20 Enrolled in 1st treatment phase: 10 in modafinil, 10 in placebo</td>
<td>Withdrawn NR Lost to followup NR 20 (100%) analyzed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean GSI score 1.6</td>
<td></td>
<td>Analysis of 1st treatment phase included 10 in modafinil, 10 in placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean education 13.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Subjects were matched for age, NART verbal IQ, education level, and GSI, previous use of stimulant medication, current use of stimulant medication</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood,</td>
<td>1976</td>
<td>U.K.</td>
<td>Fair</td>
<td>Self-rating Responses of Double-Blind Trial (n=11) of Methylphenidate vs Placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methylphenidate vs Placebo; p-Value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Happy-Sad: 1.37 vs 2.66; pNS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Calm-Nervous: 2.15 vs 3.60; p=.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Energetic-Tired: 1.66 vs 3.25; p=.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concentrating Mind-Wandering Mind: 1.75 vs 3.28; p=.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cool-Tempered-Hot-Tempered: 1.65 vs 3.55; p=.01</td>
</tr>
<tr>
<td>Turner,</td>
<td>2004</td>
<td>U.K.</td>
<td>Fair</td>
<td>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:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Immediate PRM % correct 91.25 vs 91.25 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Immediate PRM response latency 1889 vs 1714 ms (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Delayed PRM % correct 87.35 vs 79.8 (p=0.016); response latency in ms 2340 vs 1769 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DMTS latency 5057 vs 4121 ms (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NTOL mean attempts (all moves) 7.22 vs 7.86 (p=0.009)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RVIP mean latency 439 vs 434 ms (ns); response bias (B) 0.83 vs 0.97 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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)</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood</td>
<td>1976</td>
<td>U.K.</td>
<td>Fair</td>
<td>self-report, results on questionnaire data</td>
<td>No adverse effects reported, no response to meds: n=1</td>
</tr>
</tbody>
</table>

**Modafinil**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner</td>
<td>2004</td>
<td>U.K.</td>
<td>Fair</td>
<td>Subjective measures were self-rated on 16 measures. Blood pressure and pulse were taken before drug administration and at 2, 3, and 4 hours after drug administration.</td>
<td>NR</td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Modafinil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wood</td>
<td>1976</td>
<td>U.K. (Fair)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>By treatment, total withdrawals; withdrawals due to adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0/0</td>
</tr>
<tr>
<td>Turner</td>
<td>2004</td>
<td>U.K. (Fair)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Modafinil vs placebo, Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Run-in/ Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender, 1985</td>
<td>U.S. (Fair)</td>
<td>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.</td>
<td>Run-in NR; 1-week washout between treatment phases</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender,</td>
<td>1985</td>
<td>U.S. (Fair)</td>
<td>Clinical status was evaluated at beginning of each treatment phase, 1 week following initiation, and at end of 2-week drug or placebo phase. Physician's target symptom rating scale Physician's Global Rating Scale Medicine response sheet (self-rating instrument) Global Assessment Scale Profile of Mood States SCL-90</td>
<td>Mean age 31.1 54% male</td>
<td>Ethnicity NR</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Other population characteristics</th>
<th>Number screened/ enrolled/ analyzed: N per drug</th>
<th>Number withdrawn/ lost to fu/ analyzed: N per drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender,</td>
<td>1985</td>
<td>U.S. (Fair)</td>
<td>Comorbidities: 68% dysthymic disorder 22% cyclothymic disorder</td>
<td>NR/NR/37 Same subjects exposed to both treatments</td>
<td>0% withdrawn; 0% lost to followup; 37 (100%) analyzed, N per drug not reported (phases were combined in analysis).</td>
</tr>
</tbody>
</table>
**Evidence Table 11. Placebo-controlled trials in adults with ADHD**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Results</th>
</tr>
</thead>
</table>
| Wender, 1985 | U.S. (Fair) | Physician's Global Rating scale 1.4 vs 0.16 (p<0.005) | Final physician and patient ratings, methylphenidate vs placebo:  
  Physician's Global Rating scale 1.4 vs 0.16 (p<0.005)  
  Global Assessment Scale 69.17 vs 61.26 (p<0.005)  
  Physician's target symptom ratings (1=none, 4=marked):  
  hyperactivity 2.33 vs 3.29 (p<0.005); short attention span 2.27 vs 3.35 (p<0.0005); mood problems 2.36 vs 3.14 (p<0.005); anger 2.35 vs 3.11 (p<0.01); disorganization 2.12 vs 3.03 (p<0.005); conduct disorder 1.42 vs 1.67 (ns)  
  Patient's subjective experience (1=absent, 5=very much):  
  nervous 2.56 vs 2.97 (ns); happy 3.16 vs 2.70 (p<0.05); energetic 3.27 vs 3.11 (ns); mind wandering 2.37 vs 2.97 (p<0.025); hot tempered 2.32 vs 2.43 (ns); calm 2.83 vs 2.35 (ns); sad 1.81 vs 2.10 (ns);  
  tired/sleepy 1.88 vs 2.28 (ns); concentrating 2.86 vs 2.41 (ns); hungry 1.97 vs 2.51 (p<0.025); cool tempered 3.97 vs 2.44 (p<0.025); global 4.97 vs 4.31 (ns)  
  Profile of mood states:  
  tension-anxiety 49.06 vs 55.71 (p<0.001); depression-dejection 43.88 vs 50.50 (p<0.001); anger-hostility 50.34 vs 57.03 (p<0.01);  
  vigor 70.40 vs 66.53 (ns); fatigue 48.00 vs 53.47 (p<0.05); confusion 51.53 vs 58.25 (p<0.001)  
  BDI 8.94 vs 9.23 (ns) |
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender</td>
<td>1985</td>
<td>U.S. (Fair)</td>
<td>Self-report</td>
<td>Mild anxiety, insomnia, jaw tension, tooth grinding, overtimulation, irritability, nose tingling</td>
</tr>
</tbody>
</table>


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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>By treatment, total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender, 1985</td>
<td>U.S.</td>
<td>Fair</td>
<td>Methylphenidate vs placebo: Total withdrawals 0 vs 0 Withdrawals due to AEs 0 vs 0</td>
<td>Data from the first phase was not reported separately. Outcomes were presented as combined data from phases of each drug.</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Interventions (drug, regimen, duration)</th>
<th>Run-in/ Washout Period</th>
<th>Allowed other medications/ interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender, 1981</td>
<td>U.S. (Fair)</td>
<td>Pemoline or placebo was dispensed in identical 37.5 mg tablets. Initial dose was 18.75 mg, and increased by this amount every 3 to 7 days, based on patient's response. Maximum daily dose was set at 4 tablets = 150 mg/day. The entire daily dose was given once per day in the morning.</td>
<td>NR/NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemoline mean dose 71 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo mean dose 101 mg/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration 6 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilens, 1999</td>
<td>U.S. (Fair)</td>
<td>Pemoline or placebo (in 18.75 and 37.5 mg capsules) were prescribed in once-daily doses. Study medication was titrated up to 1 mg/kg/day by end of week 1, to 2 mg/kg/day by week 2, and to 3 mg/kg/day by week 3.</td>
<td>Run-in NR; 2-week washout between treatment phases</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pemoline mean dose at end of week 4: 2.2 mg/kg/day (148 mg/day).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo mean dose NR.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration 10 weeks: two 4-week treatment periods separated by 2-week washout. Treatment order was randomized</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>Method of Outcome Assessment and Timing of Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemoline</td>
<td></td>
<td></td>
<td></td>
<td>Baseline characteristics were determined using WAIS, SCL-90, Minnesota Multiphasic Personality Inventory; GAS; WRAT (assess reading, spelling, &amp; arithmetic skills), Lincoln-Oseretsky Test (a battery of motor tasks that assesses coordination); Porteus Maze; Embedded Figures Test; Physicians' Global Assessment of Change; Physicians' Global Rating of Change</td>
<td>Mean age 28.3</td>
<td>46% female</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>1981</td>
<td>U.S.</td>
<td>(Fair)</td>
<td><strong>Patient's clinical status was evaluated over the course of the trial using 3 instruments:</strong>&lt;br&gt;1) The Medicine Response Sheet&lt;br&gt;2) The Physician Target Symptom Scale&lt;br&gt;3) The Physicians' Global Assessment of Change&lt;br&gt;Presence of hyperactivity in childhood was assessed by parents using PRS.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilens</td>
<td>1999</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>ADHD Symptom Checklist; CGI Severity &amp; Improvement. Improvement defined as 30% reduction in symptoms.&lt;br&gt;Neuropsychologic test battery was administered three times: at baseline and after each arm of the study, and included an auditory version of the CPT, the Stroop test, the computerized WCST, the scattered letters version of the visual cancellations test, and the ROCFT.</td>
<td>Mean age 40.7</td>
<td>68.6% male</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>(Quality Score)</th>
<th>Other population characteristics</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed: N per drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender,</td>
<td>1981</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Mean GAS rating 56 (moderately severe psychopathology) Alcohol abuse: 6 Drug abuse: 6 Brouet's syndrome: 2 probable Antisocial personality: 3 definite, 4 probable Generalized anxiety disorder: 13 definite, 2 probable Dysphoric disorders: 21 patients All but one of the female subjects had dysphoric disorders, and half had alcoholic fathers. Among the patients' 34 children, 41% had been independently identified as hyperactive.</td>
<td>NR/60/48</td>
<td>6 (12.5%) withdrawn; 6 (12.5%) withdrawn; Lost to followup NR; 47 (98%) analyzed: 26 subjects had PRS scores &gt;=12 indicating childhood symptoms, and were considered true hyperactives. In the subsample (n=26) of true hyperactives: Pemoline n=17 Placebo n=9</td>
</tr>
<tr>
<td>Wilens,</td>
<td>1999</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>All subjects had at least one previous comorbid psychiatric disorder; for 57% the comorbid disorder was also present within the past month. Comorbid disorders (lifetime) Antisocial disorder 17% Major depression 40% Dysthymia 15% Bipolar disorder 0% Multiple anxiety disorders 28% Social phobia 29% Generalized anxiety disorder 15% Bulimia 3% Obsessive-compulsive disorder 0% Smoking 40% Alcohol abuse or dependence 59% Drug abuse or dependence 59%</td>
<td>151/35/35 N per drug in 1st phase not reported</td>
<td>8 (23%) withdrawn 8 (23%) withdrawn Lost to followup NR 35 (100%) analyzed; N per drug not reported (phases were combined in analysis)</td>
</tr>
</tbody>
</table>
Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender,</td>
<td>1981</td>
<td>U.S. (Fair)</td>
<td>Physicians’ Global Assessment of Change: % of all 48 patients (with or without childhood symptoms), pemoline vs placebo, p-values not reported:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+3 (marked improvement) = 23 vs 18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+2 (moderate improvement) = 15 vs 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+1 (mild improvement) = 27 vs 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0 (worsening) = 35 vs 55%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The following results are among true (childhood-onset) hyperactives (pemoline n=17; placebo n=9):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+3 = 29.4 vs 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+2 = 17.6 vs 11.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+1 = 17.6 vs 0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 (no change) = 17.6 vs 66.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-1 (mild worsening) = 17.6 vs 11.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-2 (moderate worsening) = 0 vs 11.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Change in Physicians’ Global Assessment, pemoline vs placebo:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High score on PRS: -0.1 vs +1.25 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low score on PRS: +1.15 vs +1.35 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Change in target-symptom ratings, pemoline vs placebo:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Motor hyperactivity -0.94 vs -0.11 (p=0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Attentional difficulties -0.64 vs 0.11 (p=0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Affective liability -0.53 vs -0.33 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inability to complete tasks -0.78 vs -0.22 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hot temper -1.18 vs -0.11 (p&lt;0.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impaired interpersonal relationships -0.59 vs 0 (ns)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impulsivity -0.88 vs 0.34 (p=0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stress intolerance -0.77 vs 0.12 (p=0.01)</td>
</tr>
</tbody>
</table>

| Wilens,  | 1999 | U.S. (Fair)             | Pemoline vs placebo:                                                                               |
|          |      |                         | Change in DSM-III-R ADHD symptoms checklist score: -7.5 vs -1 (p=0.015)                            |
|          |      |                         | % of subjects who improved by 30% reduction in symptoms: 50% vs 17% (p=0.008)                       |
|          |      |                         | CGI Improvement score of 1 or 2 (much to very much improved), by timepoint:                         |
|          |      |                         | Week 1: 7% vs 9% (ns)                                                                             |
|          |      |                         | Week 2: 24% vs 3% (p=<0.06)                                                                        |
|          |      |                         | Week 3: 33% vs 21% (ns)                                                                            |
|          |      |                         | Week 4: 38% vs 14% (p=<0.05)                                                                       |
|          |      |                         | Reduction in ADHD symptoms at endpoints, week 4 and 10, p-value signifying change from baseline: 28% (p=0.0001) vs 10% (ns) |
|          |      |                         | Neuropsychologic test results: no difference between pemoline and placebo in the aggregate or on the individual tests, including CPT, Stroop, WCST, scattered letters version of the visual cancellations test, and ROCFT. Results not shown. |
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender,</td>
<td>1981</td>
<td>U.S. (Fair)</td>
<td>Elicited by investigator in an open-ended fashion</td>
<td>54% in pemoline and 1 in placebo complained of moderate to severe side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N subjects in pemoline group, :</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Headache n=7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abdominal symptoms (nausea, cramping, anorexia) n=5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insomnia n=6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anxiety n=2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intensification of symptoms n=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Confusion and depersonalization n=1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prodromal psychosis with loosening of associations, increased anxiety, and possible ideas of reference =1.</td>
</tr>
<tr>
<td>Wilens,</td>
<td>1999</td>
<td>U.S. (Fair)</td>
<td>% of patients who experienced at least one adverse effect, pemoline vs placebo: 24% vs 12% (p&lt;0.0006)</td>
<td>1 subject on pemoline showed increased lactic dehydrogenase levels for 4 months and a marked decrease in polymorphic leukocyte counts for another 4 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SGOT analyses to assess liver function were performed at baseline and at end of weeks 4 and 10.</td>
<td>On pemoline:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mandibular joint 17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dry mouth 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dysphoria 8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased appetite 8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>On placebo:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mandibular joint 17%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dry mouth 14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dysphoria 8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decreased appetite 8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>One patient developed a mild tic that persisted at 1-year follow-up</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Pemoline</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender,</td>
<td>1981</td>
<td>U.S.</td>
<td>Fair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilens,</td>
<td>1999</td>
<td>U.S.</td>
<td>Fair</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Pemoline

<table>
<thead>
<tr>
<th>Treatment, total withdrawals; withdrawals due to adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemoline vs placebo, Total withdrawals: 5 (19%) vs 1 (4.5%)</td>
<td>This study enrolled adults with ADD symptoms, irrespective of childhood onset. The report provides separate results of the subsample of patients who were considered true hyperactives based on parent rating scale.</td>
</tr>
<tr>
<td>4 (15.4%) vs 0%</td>
<td></td>
</tr>
<tr>
<td>Pemoline vs placebo, Total withdrawals: 4 (11.4%) vs 3 (8.6%); 1 (2.9%) treatment NR</td>
<td>Data from the first phase was not reported separately. An order-effects analysis found no significant order effect.</td>
</tr>
<tr>
<td>4 (11.4%) vs 0%</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>Wilens,</td>
<td>1999</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>Wilens,</td>
<td>1999</td>
</tr>
</tbody>
</table>
### Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Number screened/eligible/enrolled</th>
<th>Number withdrawn/lost to fu/analyzed: N per drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilens,</td>
<td>1999</td>
<td>U.S.</td>
<td>Fair</td>
<td>151/35/35</td>
<td>8 (23%) withdrawn</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N per drug in 1st phase not reported</td>
<td>Lost to followup NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35 (100%) analyzed;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N per drug not reported (phases were combined in analysis)</td>
</tr>
</tbody>
</table>

**Other population characteristics**

- All subjects had at least one previous comorbid psychiatric disorder; for 57% the comorbid disorder was also present within the past month.
- Comorbid disorders (lifetime)
  - Antisocial disorder 17%
  - Major depression 40%
  - Dysthymia 15%
  - Bipolar disorder 0%
  - Multiple anxiety disorders 28%
  - Social phobia 29%
  - Generalized anxiety disorder 15%
  - Bulimia 3%
  - Obsessive-compulsive disorder 0%
  - Smoking 40%
  - Alcohol abuse or dependence 59%
  - Drug abuse or dependence 59%
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Quality Score</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilens</td>
<td>1999</td>
<td>U.S.</td>
<td>Fair</td>
<td></td>
</tr>
</tbody>
</table>

**Pemoline vs placebo:**
- **Change in DSM-III-R ADHD symptoms checklist score:** -7.5 vs -1 (p=0.015)
- **% of subjects who improved by 30% reduction in symptoms:** 50% vs 17% (p=0.008)
- **CGI Improvement score of 1 or 2 (much to very much improved), by timepoint:**
  - Week 1: 7% vs 9% (ns)
  - Week 2: 24% vs 3% (p<=0.06)
  - Week 3: 33% vs 21% (ns)
  - Week 4: 38% vs 14% (p<=0.05)

**Reduction in ADHD symptoms at endpoints, week 4 and 10, p-value signifying change from baseline:** 28% (p=0.0001) vs 10% (ns)

**Neuropsychologic test results:** no difference between pemoline and placebo in the aggregate or on the individual tests, including CPT, Stroop, WCST, scattered letters version of the visual cancellations test, and ROCFT. Results not shown.
## Evidence Table 11. Placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country (Quality Score)</th>
<th>Method of adverse effects assessment</th>
<th>Adverse Effects Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilens, 1999</td>
<td>U.S. (Fair)</td>
<td>% of patients who experienced at least one adverse effect, pemoline vs placebo: 24% vs 12% (p&lt;0.0006)</td>
<td>On pemoline: Mandibular joint 17% Dry mouth 14% Dysphoria 8% Decreased appetite 8% 12 on pemoline and 4 on placebo had dose lowered because of AEs One patient developed a mild tic that persisted at 1-year follow-up</td>
<td></td>
</tr>
</tbody>
</table>
|        |      | SGOT analyses to assess liver function were performed at baseline and at end of weeks 4 and 10. | }
**Evidence Table 11. Placebo-controlled trials in adults with ADHD**

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

Withdrawals due to AEs:
4 (11.4%) vs 0%
### Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

#### Internal Validity

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Randomization adequate?</th>
<th>Allocation concealment adequate?</th>
<th>Groups similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Outcome assessors masked?</th>
<th>Care provider masked?</th>
<th>Patient masked?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouffard, 2003</td>
<td>No (numbers chosen from a hat)</td>
<td>No (see comment in Evidence Table)</td>
<td>Not reported by phase; same subjects exposed to both treatments</td>
<td>Yes</td>
<td>Yes but method not described</td>
<td>NR</td>
<td>Yes but method not described</td>
</tr>
<tr>
<td>Cox, 2000</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Yes, except for history of moving violations and car crashes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gualtieri, 1985</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Not reported by phase; same subjects exposed to both treatments</td>
<td>Yes</td>
<td>Yes but method not described</td>
<td>NR</td>
<td>Yes but method not described</td>
</tr>
<tr>
<td>Kinsbourne, 2001</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Not reported by phase; same subjects exposed to both treatments</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Levin, 2001</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mattes, 1984</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Not reported by phase; same subjects exposed to both treatments</td>
<td>Yes</td>
<td>Yes but method not described</td>
<td>NR</td>
<td>Yes but method not described</td>
</tr>
</tbody>
</table>
Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Reporting of attrition, crossovers, adherence, and contamination</th>
<th>Loss to follow-up: differential/ high</th>
<th>Intention-to-treat (ITT) analysis; if No: % analyzed</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouffard, 2003</td>
<td>Yes</td>
<td>No/ no</td>
<td>No: 79%</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cox, 2000</td>
<td>Yes</td>
<td>No/ no</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gualtieri, 1985</td>
<td>NR</td>
<td>No/ no</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kinsbourne, 2001</td>
<td>Yes</td>
<td>No/ no</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Levin, 2001</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mattes, 1984</td>
<td>Yes</td>
<td>No/ no</td>
<td>No: 92%</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
### Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

**External Validity**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouffard, 2003</td>
<td>93/NR/38 Same subjects exposed to both treatments</td>
<td>Excluded psychiatric conditions that better accounted for their current symptoms or required other treatment; substance abuse in preceding 6 months; medical condition contraindicating stimulants (that is, hypertension or cardiac disease)</td>
</tr>
<tr>
<td>Cox, 2000</td>
<td>NR/NR/13 Same subjects exposed to both treatments</td>
<td>Excluded major psychiatric illness and Tourette's disease (screened using SCID), and active (past 12 month) substance abuse using the Michigan Alcoholism Screening Test and a urine drug screen.</td>
</tr>
<tr>
<td>Gualtieri, 1985</td>
<td>NR/NR/8 Same subjects exposed to both treatments</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kinsbourne, 2001</td>
<td>NR/NR/17 Same subjects exposed to all treatments</td>
<td>Not reported</td>
</tr>
<tr>
<td>Levin, 2001</td>
<td>NR/NR/40 Placebo patch + placebo pill, n=10 Nicotine, n=10 Methylphenidate, n=10 Nicotine + methylphenidate, n=10</td>
<td>Participants with diagnoses of major depressive disorder or generalized anxiety disorder were excluded; medical exclusion criteria covered all relevant concerns for use of nicotine in a transdermal patch form: hypertension, cardiac disease, cerebrovascular disease, impaired renal function, history of seizure, skin disease, sensitivity to medical dressings or tapes, and history of skin allergies</td>
</tr>
<tr>
<td>Mattes, 1984</td>
<td>2829/116/66 Same subjects exposed to both treatments</td>
<td>Excluded patients who met DSM-III criteria for schizophrenia, major affective disorder except a major depressive episode of mild severity, any other psychosis, mental retardation (mild or worse), organic brain syndrome, or current drug or alcohol dependence (drug or alcohol abuse was allowed).</td>
</tr>
</tbody>
</table>
Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

**External Validity**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Run-in/Washout</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouffard, 2003</td>
<td>3-day run-in of increasing dosages (15/30/45 mg/day); 5 to 7-day washout btw. active &amp; placebo phases</td>
<td>No</td>
<td>Yes</td>
<td>FRSQ grant</td>
<td>Yes</td>
</tr>
<tr>
<td>Cox, 2000</td>
<td>NR/NR</td>
<td>No</td>
<td>Yes</td>
<td>University of Virginia Health Sciences Center grant</td>
<td>Yes</td>
</tr>
<tr>
<td>Gualtieri, 1985</td>
<td>Run-in NR; 68-hr washout between treatment phases</td>
<td>No</td>
<td>Yes</td>
<td>USPHS Grant HD-10570</td>
<td>Yes</td>
</tr>
<tr>
<td>Kinsbourne, 2001</td>
<td>NR/NR</td>
<td>No</td>
<td>Yes</td>
<td>Not reported</td>
<td>Yes</td>
</tr>
<tr>
<td>Levin, 2001</td>
<td>NR/NR</td>
<td>Unclear</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Mattes, 1984</td>
<td>NR/NR</td>
<td>No</td>
<td>Yes</td>
<td>Public Health Service grant</td>
<td></td>
</tr>
</tbody>
</table>
# Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

## Internal Validity

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Randomization adequate?</th>
<th>Allocation concealment adequate?</th>
<th>Groups similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Outcome assessors masked?</th>
<th>Care provider masked?</th>
<th>Patient masked?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson, 2003</td>
<td>Yes</td>
<td>Method NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Paterson, 1999</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes but method not described</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Schubiner, 2002</td>
<td>NR</td>
<td>NR</td>
<td>No; MPH&gt;placebo in ASI psychiatric composite scores</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Spencer, 1995</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Not reported by phase; same subjects exposed to both treatments</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Spencer, 1998</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Not reported by phase; same subjects exposed to both treatments</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

#### Internal Validity

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Reporting of attrition, crossovers, adherence, and contamination</th>
<th>Loss to follow-up: differential/high</th>
<th>Intention-to-treat (ITT) analysis; if No; % analyzed</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson, 2003</td>
<td>Yes, NR, NR, NR</td>
<td>No/ no</td>
<td>No: 96%</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Paterson, 1999</td>
<td>Yes, Yes, Yes</td>
<td>No/ no</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Schubiner, 2002</td>
<td>Yes, NR, NR, NR</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Spencer, 1995</td>
<td>Yes, NR, NR, NR</td>
<td>No/ no</td>
<td>No: 92%</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Spencer, 1998</td>
<td>Yes, NR, NR, NR</td>
<td>No/ no</td>
<td>No: 95.4%</td>
<td>No</td>
<td>Fair</td>
</tr>
</tbody>
</table>
### Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

#### External Validity

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number screened/eligible/enrolled</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Michelson, 2003</strong></td>
<td>448/329/280 Atomoxetine n=141 Placebo n=139 388/325/256 Atomoxetine n=129 Placebo n=127</td>
<td>Excluded patients with current major depression or anxiety disorder; patients with current or past bipolar or psychotic disorders; patients with serious medical illness; patients who met DSM-IV criteria for alcohol dependence. Patients actively using recreational drugs at time of study entry were excluded. Urine screening for drugs of abuse was performed at the initial visit, and could be repeated during the trial at the investigator’s discretion.</td>
</tr>
<tr>
<td><strong>Paterson, 1999</strong></td>
<td>68/51/45 24 dexamphetamine 21 placebo</td>
<td>Patients were excluded if they had an insufficient ADHD score, or comorbidity for other major psychiatric disorders, including a history of current substance abuse. Organic disorders that would contraindicate the use of dexamphetamine were also excluded.</td>
</tr>
<tr>
<td><strong>Schubiner, 2002</strong></td>
<td>932/338/59 Methylphenidate n=24 Placebo n=24 Pemoline n=11 (dropped from analysis)</td>
<td>Less than an estimated IQ of 75 on the Shipley Institute of Living scale; schizophrenia, bipolar disorder, dementia, and delirium</td>
</tr>
<tr>
<td><strong>Spencer, 1995</strong></td>
<td>85/25/25 N per drug during first phase not reported.</td>
<td>Excluded prospective subjects if they had any clinically significant chronic medical conditions or abnormal baseline laboratory values or a history of tic disorders, mental retardation (IQ &lt;75), organic brain disorders, clinically unstable psychiatric conditions (ie, suicidal behaviors, psychosis, delinquency, criminality, or violence), or substance or alcohol abuse or dependence within the 6 months preceding the study or currently used psychotropics; also excluded pregnant or nursing women.</td>
</tr>
<tr>
<td><strong>Spencer, 1998</strong></td>
<td>NR/NR/22</td>
<td>Exclusion criteria include clinically significant chronic medical conditions, abnormal baseline laboratory values, mental retardation (IQ&lt;75), organic brain disorders, clinically unstable active psychiatric conditions, drug or alcohol abuse within the last 6 months, current use of psychotropics, and for women, pregnancy or nursing.</td>
</tr>
</tbody>
</table>
### Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

#### External Validity

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Run-in/Washout</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michelson, 2003</td>
<td>1-week washout, followed by 2-week placebo lead-in phase</td>
<td>No</td>
<td>Yes</td>
<td>Eli Lilly</td>
<td>Yes</td>
</tr>
<tr>
<td>Paterson, 1999</td>
<td>NR/NR</td>
<td>No</td>
<td>Yes</td>
<td>Health Department of Western Australia</td>
<td>Yes</td>
</tr>
<tr>
<td>Schubiner, 2002</td>
<td>NR/NR</td>
<td>Unclear</td>
<td>Yes</td>
<td>National Institute on Drug Abuse Grant R01 DA 10271-03 and a Joe Young Srs. Research grant from the State of Michigan</td>
<td>Yes</td>
</tr>
<tr>
<td>Spencer, 1995</td>
<td>Run-in NR; 1-week washout between phases</td>
<td>No</td>
<td>Yes</td>
<td>Not reported</td>
<td>Yes</td>
</tr>
<tr>
<td>Spencer, 1998</td>
<td>Run-in NR; 1-week washout between phases</td>
<td>NR</td>
<td>Yes</td>
<td>&quot;Funded in part by Lilly Research Labs&quot; and an NIMH grant</td>
<td>Yes</td>
</tr>
</tbody>
</table>
## Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

### Internal Validity

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Randomization adequate?</th>
<th>Allocation concealment adequate?</th>
<th>Groups similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Outcome assessors masked?</th>
<th>Care provider masked?</th>
<th>Patient masked?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer, 2001</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Not reported by phase; same subjects exposed to both treatments</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Spencer, 2005</td>
<td>Method NR</td>
<td>Method NR</td>
<td>No - MPH group younger</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tenenbaum, 2002</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Not reported</td>
<td>Yes</td>
<td>Yes but method not described</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Turner, 2004</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes but method not described</td>
<td>Not reported</td>
<td>Yes but method not described</td>
</tr>
<tr>
<td>Wender, 1981</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Not reported</td>
<td>Yes</td>
<td>Yes but method not described</td>
<td>Not reported</td>
<td>Yes but method not described</td>
</tr>
</tbody>
</table>
### Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

#### Internal Validity

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Reporting of attrition, crossovers, adherence, and contamination</th>
<th>Loss to follow-up: differential/high</th>
<th>Intention-to-treat (ITT) analysis; if No: % analyzed</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer, 2001</td>
<td>Yes</td>
<td>No/ no</td>
<td>No: 90%</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Spencer, 2005</td>
<td>Yes</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>Poor</td>
</tr>
<tr>
<td>Tenenbaum, 2002</td>
<td>Yes</td>
<td>No/ no</td>
<td>No: 72.7%</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Turner, 2004</td>
<td>Yes</td>
<td>No/ no</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Wender, 1981</td>
<td>Yes</td>
<td>No/ no</td>
<td>Unclear</td>
<td>No</td>
<td>Fair</td>
</tr>
</tbody>
</table>
## Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

### Exclusion criteria

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number screened/ eligible/ enrolled</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer, 2001</td>
<td>103/41/30 Same subjects exposed to both treatments</td>
<td>Excluded clinically significant chronic medical conditions, abnormal baseline laboratory values, IQ less than 80, delirium, dementia, or amnestic disorders, any other clinically unstable psychiatric conditions (i.e. bipolar disorder, psychosis), drug or alcohol abuse or dependence within the 6 months preceding the study, previous adequate trial of Adderall, or current use of psychotropics; also excluded pregnant or nursing females.</td>
</tr>
<tr>
<td>Spencer, 2005</td>
<td>289/NR/146</td>
<td>Subjects had clinically significant chronic medical conditions; abnormal baseline laboratory value; IQ&lt;80; delirium, dementia, or amnestic disorders; other clinically unstable psychiatric conditions (i.e. bipolar disorder, psychosis, suicidality); drug or alcohol abuse or dependence within the 6 months preceding the study; previous adequate trial of stimulant (&gt;0.5mg/kg/day of MPH or equivalent); or current use of other psychotropics. Pregnant or nursing women were also excluded.</td>
</tr>
<tr>
<td>Tenenbaum, 2002</td>
<td>128/85/33 Same subjects exposed to all treatments.</td>
<td>Potential participants were excluded if they had any clinically significant medical conditions such as heart condition, untreated thyroid condition, or tic disorder. Participants with active substance or alcohol abuse/dependence in the 6 months prior were also excluded. Other exclusions: pregnant or nursing females; neurological trauma or disorder (eg. concussion, epilepsy); chronic diseases; poor physical health; poor vision unless corrected. Individuals taking psychoactive medications (including methylphenidate) were excluded unless they discontinued such medications under the supervision of their prescribing physician for the duration of the study. Also excluded clients at the Attention Deficit Center, where all assessment and treatment sessions were conducted, due to potential conflict of interest. Excluded psychiatric disorders for which treatment with methylphenidate was contraindicated (e.g. panic disorder, major depression, moderate or more severe) or they were clinically unstable (e.g. suicidal behavior, psychosis, criminality/violence, bipolar disorder).</td>
</tr>
<tr>
<td>Turner, 2004</td>
<td>NR/NR/20 Enrolled in 1st treatment phase: 10 in modafinil, 10 in placebo</td>
<td>NART verbal IQ score &lt;90, any significant visual or motor impairment, or the use of any medication contraindicated with modafinil. Patients were required to have no history of pervasive developmental disorders, neurologic disorders (including tic disorders), schizophrenia or psychotic disorders, bipolar disorder, or current major depressive disorder. Patients reported no substance abuse in the past 2 months. In addition, patients with a history of hypertension, cardiac disorder, or epilepsy. Patients were advised not to consume alcohol or caffeine for 12 hours before the study.</td>
</tr>
<tr>
<td>Wender, 1981</td>
<td>NR/60/48 Pemoline n=26 Placebo n=22</td>
<td>Excluded DSM-III diagnoses of schizophrenia, schizoaffective disorder, primary affective disorder, schizotypal personality, or &quot;borderline&quot; personality; excluded organic brain syndrome and mental retardation. Excluded patients who reported that they had taken stimulant medication or &quot;diet pills&quot; in the past and that they had been stimulated, excited, or &quot;wired&quot; by such medication. Excluded gravid or lactating females. Excluded medical contraindications to stimulant drug therapy.</td>
</tr>
</tbody>
</table>
### Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

**External Validity**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Run-in/Washout</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spencer, 2001</td>
<td>Run-in NR; 1-week blinded placebo washout between phases</td>
<td>No</td>
<td>Yes</td>
<td>Shire Richwood Pharmaceuticals; NIMH grant</td>
<td>Yes</td>
</tr>
<tr>
<td>Spencer, 2005</td>
<td>NR/NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NIMH and Novartis</td>
<td>Yes</td>
</tr>
<tr>
<td>Tenenbaum, 2002</td>
<td>Run-in NR; 1-week washout between treatment phases</td>
<td>No, but excluded current use of MPH unless use was discontinued</td>
<td>Yes</td>
<td>Henkel Corporation</td>
<td>Yes</td>
</tr>
<tr>
<td>Turner, 2004</td>
<td>Run-in NR; 1-week washout between single-dose treatment phases</td>
<td>No</td>
<td>Yes</td>
<td>Wellcome Trust Program grant</td>
<td>Yes</td>
</tr>
<tr>
<td>Wender, 1981</td>
<td>NR/NR</td>
<td>No</td>
<td>Yes</td>
<td>Abbott Laboratories; NIMH grant</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

**Internal Validity**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Randomization adequate?</th>
<th>Allocation concealment adequate?</th>
<th>Groups similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Outcome assessors masked?</th>
<th>Care provider masked?</th>
<th>Patient masked?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender, 1985</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Not reported by phase; same subjects exposed to both treatments</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Wernicke, 2004</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Not reported</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes but method not described</td>
</tr>
<tr>
<td>Wilens, 1999</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Not reported by phase; same subjects exposed to both treatments</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wilens, 2001</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Wood, 1976</td>
<td>Method NR</td>
<td>Method NR</td>
<td>Same 11 subjects in both drug groups</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
<td>Yes but method not described</td>
</tr>
</tbody>
</table>
### Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

**Internal Validity**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Reporting of attrition, crossovers, adherence, and contamination</th>
<th>Loss to follow-up: differential/high</th>
<th>Intention-to-treat (ITT) analysis; If No: % analyzed</th>
<th>Post-randomization exclusions</th>
<th>Quality Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender, 1985</td>
<td>Attrition yes</td>
<td>No/no</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Wernicke, 2004</td>
<td>Yes</td>
<td>No/no</td>
<td>No: 99.2%</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Wilens, 1999</td>
<td>Yes</td>
<td>No/no</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Wilens, 2001</td>
<td>Yes</td>
<td>No/no</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
</tr>
<tr>
<td>Wood, 1976</td>
<td>NR</td>
<td>No/no</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
</tr>
</tbody>
</table>
### Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD

#### External Validity

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Number screened/ eligible/ enrolled</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender, 1985</td>
<td>NR/NR/37 Same subjects exposed to both treatments</td>
<td>Excluded DSM-III diagnoses of schizophrenia or schizoaffective disorder, current major mood disorder, and any specific features of schizoid, schizotypal, or borderline personality disorder, such as unstable and intense interpersonal relationships with idealization and devaluation, identity disturbances, intolerance of being alone, and physically self-damaging acts, including self-mutilation and suicidal gestures.</td>
</tr>
<tr>
<td>Wernicke, 2004</td>
<td>NR/NR/380; Atomoxetine with abrupt discontinuation n=90; Atomoxetine with tapered discontinuation n=94; Placebo n=196</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wilens, 1999</td>
<td>151/35/35 N per drug in 1st phase not reported</td>
<td>Potential subjects were excluded if they had any clinically significant chronic medical conditions or clinically significant abnormal baseline laboratory liver function tests, mental retardation (IQ &lt;75), organic brain disorders, clinically unstable psychiatric conditions, bipolar or psychotic disorders, drug or alcohol abuse or dependence within the 6 months preceding the study, previous exposure to pemoline, or current use of psychotropics. Also excluded pregnant or nursing women.</td>
</tr>
<tr>
<td>Wilens, 2001</td>
<td>154/NR/40 Bupropion n=21 Placebo n=19</td>
<td>Potential subjects were excluded if they had any clinically significant chronic medical conditions or clinically significant abnormal baseline laboratory liver function tests, mental retardation (IQ &lt;75), organic brain disorders, clinically unstable psychiatric conditions, bipolar or psychotic disorders, drug or alcohol abuse or dependence within the 6 months preceding the study, or current use of psychotropics. Potential subjects with previous exposure to bupropion were also excluded.</td>
</tr>
<tr>
<td>Wood, 1976</td>
<td>NR/25/15</td>
<td>After first screening for inclusion, subjects who met the diagnosis of schizophrenia or primary affective disorders according to the Research Diagnostic Criteria of Spitzer were excluded.</td>
</tr>
</tbody>
</table>
**Evidence Table 12. Quality assessment of placebo-controlled trials in adults with ADHD**

*External Validity*

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Run-in/Washout</th>
<th>Class naïve patients only</th>
<th>Control group standard of care</th>
<th>Funding</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wender, 1985</td>
<td>Run-in NR; 1-week washout between treatment phases</td>
<td>No</td>
<td>Yes</td>
<td>NIMH grant</td>
<td>Yes</td>
</tr>
<tr>
<td>Wernicke, 2004</td>
<td>NR/NR</td>
<td>No</td>
<td>Yes</td>
<td>Eli Lilly</td>
<td>Yes</td>
</tr>
<tr>
<td>Wilens, 1999</td>
<td>Run-in NR; 2-week washout between treatment phases</td>
<td>No, but excluded previous use of trial drug</td>
<td>Yes</td>
<td>Abbott Laboratories; NIH Scientist Development Award</td>
<td>Yes</td>
</tr>
<tr>
<td>Wilens, 2001</td>
<td>NR/NR</td>
<td>No, but excluded previous use of trial drug</td>
<td>Yes</td>
<td>Glaxo Wellcome Inc.; NIH; National Institute on Drug Abuse</td>
<td>Yes</td>
</tr>
<tr>
<td>Wood, 1976</td>
<td>Run-in NR; no washout between phases of the crossover trial since MPH has &quot;a short duration of action&quot;</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Design</td>
<td>Eligibility Criteria</td>
<td>Duration</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>--------</td>
<td>----------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Paternite</td>
<td>1999</td>
<td>(Fair)</td>
<td>Descriptive study Setting: University of Iowa outpatient child psychiatry clinic</td>
<td>Patients with diagnoses of hyperkinetic reaction or a minimal brain dysfunction syndrome were treated with MPH between 1967-1972</td>
<td>Mean=30.4 months range=1-76 months</td>
</tr>
<tr>
<td>Weiss</td>
<td>1975</td>
<td>(Fair)</td>
<td>Retrospective Cohort study Setting: the psychiatry department of the Montreal children's Hospital</td>
<td>Hyperactive children initially evaluated from 1962-1967 had been treated with methylphenidate, chlorpromazine, or none (group 1, 2 and 3).</td>
<td>Group 1: 51 months Group 2: 30 months</td>
</tr>
<tr>
<td>Lerer</td>
<td>1977</td>
<td>(Fair)</td>
<td>Before-After Setting: NR</td>
<td>Hyperactive children with IQ above 80 and marked academic underachievement</td>
<td>60 days - 6 months</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Functional capacity</td>
<td>Age</td>
<td>Screened</td>
<td>Withdrawn</td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>---------------------</td>
<td>--------------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Paternite</td>
<td>1999</td>
<td>General Interview structured interview by Loney</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Fair)</td>
<td></td>
<td>Schedule of Affective Disorders and Schizophrenia (SADS-L) structured interview</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interviewer: NR</td>
<td>Mean age=8.8 years, Gender: 100% male, Ethnicity: NR</td>
<td>219/121/97</td>
<td>NR/NR/97</td>
</tr>
<tr>
<td>Weiss</td>
<td>1975</td>
<td>Academic performance (reported cards rated by teachers)</td>
<td>Mean age= 7.96, 8.15 and 8.21 years (group 1, 2 and 3), Gender: NR, Ethnicity: NR</td>
<td>NR/NR/150</td>
<td>NR/84/66</td>
</tr>
<tr>
<td>(Fair)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lerer</td>
<td>1977</td>
<td>School grades (by teachers)</td>
<td>Mean age=15.5 years, Gender: 92.6% male, Ethnicity: 100% white</td>
<td>55/27/27</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Functional capacity</td>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>---------</td>
<td>---------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Paternite</td>
<td>1999</td>
<td>(Fair)</td>
<td>Correlations with (a) &quot;MPH dosage&quot;; (b) &quot;MPH response&quot;; (c) &quot;MPH duration&quot;</td>
<td>Psychiatric hospitalizations: none</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Suicide attempts: only (a) $r = -0.23$, $p&lt;0.05$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Police contacts: none</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Emancipated living: only (b) $r=0.31$, $p&lt;0.05$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relationship commitment: only (b) $r=0.25$, $p&lt;0.05$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>High school graduation: only (b) $r = -0.34$, $p&lt;0.01$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Post-secondary education: none</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Full employment: none</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Never fired from a job: none</td>
<td></td>
</tr>
<tr>
<td>Weiss</td>
<td>1975</td>
<td>(Fair)</td>
<td>Number of children in each group passing all grades or failing one or more grades:</td>
<td>Had never failed/ Had failed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group 1: 13(54%)/11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group 2: 9(41%)/12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group 3: 6(30%)/14</td>
<td></td>
</tr>
<tr>
<td>Lerer</td>
<td>1977</td>
<td>(Fair)</td>
<td>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.</td>
<td>After 7-12 months of follow-up, only 2 have shown improvement. 3 have been temporarily or permanently suspended from school.</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Design</td>
<td>Eligibility Criteria</td>
<td>Duration</td>
<td>Interventions (mean dose)</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>-------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Hecktman</td>
<td>1984</td>
<td>Retrospective Cohort</td>
<td>6-12 years of age for sustained hyperactivity both at home and at school. Free of epilepsy, cerebral palsy, or psychosis</td>
<td>3 years between 6-12 years of age</td>
<td>MPH 20-50mg/day</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Age</td>
<td>Gender</td>
<td>Ethnicity</td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
<td>---------</td>
<td>-----</td>
<td>--------</td>
<td>-----------</td>
</tr>
<tr>
<td>Heckman</td>
<td>1984</td>
<td>(Fair)</td>
<td>NR</td>
<td>Mean age=21.8 years</td>
<td>NR/NR</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Functional capacity</td>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>---------</td>
<td>---------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Hecktman</td>
<td>1984</td>
<td>(Fair)</td>
<td>Stimulant-treated hyperactives (STH), non-STH, Matched controls (MC):</td>
<td>Demographic data:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>residential moves: STH&gt;MC, p&lt;0.05</td>
<td>live with girlfriends/wifes: STH&gt;MC, p&lt;0.02; STH&gt;non-STH, p&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>future vocational plans or lower status plans: MC&gt;STH, p&lt;0.05</td>
<td>in debt: STH&gt;MC, p&lt;0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>car accidents: non-STH&gt;STH, p&lt;0.004; STH vs MC, NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>School:</td>
<td>Employers Questionnaire</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>attending junior colleges and universities: MC&gt;STH, p&lt;0.05; STH&gt;non-STH, p&lt;0.03</td>
<td>get along with co-workers: STH&gt;non-STH, no data reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fail grades in high school, STH&gt;MC, p&lt;0.1; STH vs non-STH, NS</td>
<td>being punctual, doing assigned work adequately, getting along with supervisors, completing tasks, and being rehired: all NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>drop out school because of poor marks: STH&gt;MC, p&lt;0.08; STH vs non-STH, NS</td>
<td>Work record:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>academic standing: MC&gt;STH, p&lt;0.05; STH vs non-STH, NS</td>
<td>leave school earlier: STH&gt;MC, p&lt;0.028; STH vs non-STH, NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>be expelled: STH&gt;MC, p&lt;0.07; STH vs non-STH, NS</td>
<td>spend more time doing nothing: STH&gt;MC, p&lt;0.01; STH vs non-STH, NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>not in school because of lack of interests: non-STH&gt;STH, p&lt;0.05</td>
<td>have more job: STH&gt;MC, p&lt;0.01; STH vs non-STH, NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Employer's Questionnaire</td>
<td>incomes: STH vs MC, NS; STH vs non-STH, NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>get along with co-workers: STH&gt;non-STH, no data reported</td>
<td>greater debts: STH&gt;MC, p&lt;0.06; STH vs non-STH, NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>being punctual, doing assigned work adequately, getting along with supervisors, completing tasks, and being rehired: all NS</td>
<td>longer period at last job: non-STH&gt;STH, p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Work record:</td>
<td>no problems with concentration: non-STH&gt;STH, p&lt;0.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>leave school earlier: STH&gt;MC, p&lt;0.028; STH vs non-STH, NS</td>
<td>the percent of the work day: all NS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>spend more time doing nothing: STH&gt;MC, p&lt;0.01; STH vs non-STH, NS</td>
<td>full time jobs lasting less than 2 months, summer or part time jobs and reasons</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>have more job: STH&gt;MC, p&lt;0.01; STH vs non-STH, NS</td>
<td>for leaving jobs: all NS</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Design</td>
<td>Eligibility Criteria</td>
<td>Duration</td>
<td>Interventions (mean dose)</td>
</tr>
<tr>
<td>--------------</td>
<td>------</td>
<td>-------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Charles</td>
<td>1981</td>
<td>Cross-sectional</td>
<td>Children who had participated in a 16-week RCT of MPH vs placebo</td>
<td>4 years</td>
<td>Group 1: Stimulants &lt; 6 months</td>
</tr>
<tr>
<td>(Fair/poor)</td>
<td></td>
<td>Setting: UCLA</td>
<td></td>
<td></td>
<td>Group 2: Stimulants 6 mos to 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Department of Pediatrics</td>
<td></td>
<td></td>
<td>Group 3: Stimulants 2-3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group 4: Stimulants 3-4 years, but had discontinued ≥ 1 month prior to follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Group 5: Still on stimulants (MPH or pemoline)</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Assessment Techniques</td>
<td>Age</td>
<td>Gender</td>
</tr>
<tr>
<td>---------</td>
<td>-------</td>
<td>---------</td>
<td>-----------------------</td>
<td>-----</td>
<td>--------</td>
</tr>
<tr>
<td>Charles</td>
<td>1981</td>
<td>(Fair/poor)</td>
<td>Teachers' responses to mail-based questionnaire</td>
<td>Mean age=12 years, 3 months</td>
<td>79% male</td>
</tr>
</tbody>
</table>
## Evidence Table 13. Observational Studies - Functional Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charles</td>
<td>1981</td>
<td>(Fair/poor)</td>
<td>Group 1 vs 2 vs 3 vs 4 vs 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Teacher reports of below grade level work (% children):</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reading: 77 vs 75 vs 64 vs 73 vs 83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Spelling: 69 vs 75 vs 64 vs 55 vs 75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mathematics: 69 vs 100 vs 56 vs 73 vs 58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ability to sustain attention: 38 vs 75 vs 71 vs 73 vs 75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unclear oral language: 15 vs 12 vs 14 vs 45 vs 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Percentage of repeated grades (%): 46 vs 50 vs 36 vs 31 vs 8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Special education class placement: 31 vs 60 vs 36 vs 31 vs 58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Currently tutored: 15 vs 30 vs 14 vs 23 vs 41</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Design</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------</td>
<td>---------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Bussing 2005</td>
<td></td>
<td></td>
<td>Prospective Cohort study</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Persistence</td>
<td>Country</td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
<td>-------------</td>
<td>---------</td>
</tr>
<tr>
<td>Bussing 2005</td>
<td></td>
<td>Norbeck</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 13. Observational Studies - Functional Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bussing</td>
<td>2005</td>
<td></td>
<td>% of patients having ADHD medication at the time of phone interviews</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(T2= the second phone interview, T3= the third phone interview)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(AA=African-American, C= Caucasian)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AA girls vs AA boys vs C girls vs C boys, p value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2: 10% vs 34% vs 28% vs 42%, p=0.006, B&gt;G, AA&lt;C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T3: 15% vs 31% vs 19% vs 31%, p=0.147, B&gt;G</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T2 or T3: 15% vs 41% vs 31% vs 47%, p=0.006, B&gt;G</td>
</tr>
</tbody>
</table>

**Predictors of Medication treatment: OR, p value, (95%CI)**

**Sociodemographic**
- Gender(male): 2.75, p<0.05, (1.38-5.47)
- Race/Ethnicity(African American): 0.91(0.36-2.34)
- Age: 1.56(0.68-3.55)

**Need**
- School Refferals: 1.03(0.98-1.09)
- Impairment Score: 1.02(0.97-1.07)
- Inattentive symptoms: 1.23, p<0.05, (1.05-1.43)
- Hyperactive/Impulsive Symptoms: 1.01(0.88-1.17)
- ODD or CD comorbidity: 1.11(0.49-2.52)

**Parental Characteristics**
- Average Instrumental Network Support: 0.69, p<0.001,(0.57-0.83)
- Global Caregiver Strain: 0.99(0.81-1.20)
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Design</th>
<th>Eligibility Criteria</th>
<th>Duration</th>
<th>Interventions (mean dose)</th>
<th>Concomitant medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lage 2004</td>
<td></td>
<td>Retrospective Cohort study</td>
<td>1) Age 6-12 years at date of first prescription for XR MPH or TID IR MPH (index date); 2) patient-level data files containing information for at least 6 months before and 12 months after the index date; 3) no ADHD medications (i.e. amphetamine, dextroamphetamine, methylphenidate, imipramine, desipramine, clonidine, and bupropion) in the 6 months before the index date; and 4) no XR MPH use by the IR MPH group in the 12-month follow-up period.</td>
<td>NR</td>
<td>XR MPH</td>
<td>TID IR MPH</td>
</tr>
<tr>
<td>Marcus 2005</td>
<td></td>
<td>Retrospective Cohort study</td>
<td>Patients aged 6 to 17 years who were prescribed MPH and were eligible for California Medicaid benefits for at least 6 months preceding and 12 months following an index MPH prescription. Patients should not have a prescription claim for an ADHD medication during the 6 months preceding the index MPH prescription and did not have any inpatient claims during the follow-up period.</td>
<td>12 months</td>
<td>ER-MPH</td>
<td>IR-MPH</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Assessment Techniques</td>
<td>Age</td>
<td>Screened Eligible Enrolled</td>
<td>Withdrawn Lost to fu Analyzed</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>Lage 2004</td>
<td>NR</td>
<td>sequentially counting the unduplicated continuous prescriptions using the date of the prescription and the number of days of medications supplied</td>
<td>Mean age=9.73 years 75% male</td>
<td>NR/NR/NR</td>
<td>NR/NR/1775</td>
<td></td>
</tr>
<tr>
<td>Marcus 2005</td>
<td></td>
<td></td>
<td>Mean age: NR 70% 6-12 years 29% 13-17 years</td>
<td>NR/NR/NR</td>
<td>NR/NR/11427</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>78% male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45.3% White; 22.9% Black; 26.0% Hispanic; 5.7% Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lage 2004</td>
<td></td>
<td><strong>Treatment pattern</strong>- XR MPH vs TID IR MPH, p value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Days supplied: 186 vs 127, p&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discouinue, stopped receiving all ADJD medications prior to t+1 year-28days: 47% vs 72%, p&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Switch, stopped prescription for one ADHD medication and started rescription another: 37% vs 59%, p&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persist, no discontinuations or gap (&gt;14days): 12% vs 1%, p&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Covariates of Accident/Injury</strong>- Coefficient, Odds ratio(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>XR MPH: -0.5486, 0.578(0.353-0.945)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age(years): 0.1156, 1.123(0.994-1.267)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female: -0.9015, 0.406(0.225-0.734)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preferred provider: -0.5671, 0.567(0.365-0.882)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior accidents present: 1.0576, 2.879(0.928-8.937)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prior total cost: -0.00024, 1.000(1.000-1.000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number of chronic medications: -0.1480, 0.862(0.758-0.982)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number of diagnosis: 0.2286, 1.257(1.195-1.321)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intercept: -4.2703</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marcus 2005</td>
<td></td>
<td><strong>Mean treatment duration</strong>- ER-MPH vs IR MPH, STR(95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>total: 140.3 vs 103.4, 1.37(1.32-1.42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-12y: 149.5 vs 107.5, 1.38(1.32-1.45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>13-17y: 125.1 vs 91.3, 1.35(1.27-1.43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male: 140.9 vs 101.8, 1.40(1.34-1.46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female: 138.4 vs 109.1, 1.27(1.18-1.38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>White: 154.9 vs 116.8, 1.43(1.35-1.52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Black: 125.7 vs 90.8, 1.37(1.27-1.48)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hispanic: 126.2 vs 94.9, 1.28(1.19-1.38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other: 130.4 vs 93.9, 1.29(1.10-1.53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 14: Quality Assessment of Observational Studies - Functional Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Non-biased selection?</th>
<th>For studies with ≥ 2 groups: Similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Attrition specified?</th>
<th>Loss to follow-up specified? If yes, low overall loss to follow-up?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paternite</strong> 1999</td>
<td>No: excluded 24 (19.8%)</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Weiss</strong> 1975</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Lerer</strong> 1977</td>
<td>No: excluded 11 (41%) nonresponders</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Hecktman</strong> 1984</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Charles</strong> 1981</td>
<td>No: excluded 36 (36.7%)</td>
<td>n/a</td>
<td>No</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
## Evidence Table 14: Quality Assessment of Observational Studies - Functional Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Outcomes pre-specified and defined?</th>
<th>Ascertainment techniques adequately described?</th>
<th>Non-biased and adequate ascertainment methods?</th>
<th>Statistical analysis of potential confounders?</th>
<th>Adequate duration of follow-up?</th>
<th>Overall quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional capacity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paternite</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weiss</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>NR</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>1975</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lerer</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>NR</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>1977</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hecktman</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>1984</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charles</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Fair-Poor</td>
</tr>
<tr>
<td>1981</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 14: Quality Assessment of Observational Studies - Functional Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Non-biased selection?</th>
<th>For studies with ≥ 2 groups: Similar at baseline?</th>
<th>Eligibility criteria specified?</th>
<th>Attrition specified?</th>
<th>Loss to follow-up specified? If yes, low overall loss to follow-up?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Persistence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lage 2004</td>
<td>Yes</td>
<td>No; XR group older, more HMO use, more chronic medications and diagnoses, and higher prior total medical costs</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Marcus 2005</td>
<td>Unclear</td>
<td>No; ER group patients received treatment for a mental disorder other than ADHD during the 6 months preceding the index prescription and more likely to have been prescribed antidepressants, antipsychotic medications, and mood stabilizers during the follow-up period</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Bussing 2005</td>
<td>Yes</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
## Evidence Table 14: Quality Assessment of Observational Studies - Functional Outcomes

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Persistence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lage 2004</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Marcus 2005</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
<tr>
<td>Bussing 2005</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Eligibility Criteria</th>
<th>Duration</th>
<th>Interventions (mean dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elementary School Children - Atomoxetine (tomoxetine)</td>
<td>Kratochvil 2001</td>
<td>U.S.</td>
<td>Before-after, prospective</td>
<td>1 of 24 clinical research sites involved in an ongoing multicenter study</td>
<td>DSM-IV criteria for ADHD</td>
<td>Tomoxetine mean dose nr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Setting: 1 of 24 clinical research sites involved in an ongoing multicenter study</td>
<td>DSM-IV criteria for ADHD</td>
<td>10 weeks</td>
<td>Tomoxetine mean dose nr</td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Concomitant medication</th>
<th>Safety Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Screened</th>
<th>Eligible</th>
<th>Enrolled</th>
<th>Withdrawn</th>
<th>Lost to fu</th>
<th>Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kratochvil</td>
<td>2001</td>
<td>U.S.</td>
<td>NR</td>
<td>Weight measured at weekly clinic visits</td>
<td>Mean age nr</td>
<td>100% male</td>
<td>90% white</td>
<td>NR/NR/100</td>
<td>10 analyzed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Elementary School Children - Atomoxetine (atomoxetine)**
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Safety Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kratochvil</td>
<td>2001</td>
<td>U.S.</td>
<td>Weight change (mean change): -0.15 kg, p=NS</td>
<td></td>
</tr>
</tbody>
</table>
## Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Eligibility Criteria</th>
<th>Duration</th>
<th>Interventions (mean dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brehaut</td>
<td>2003</td>
<td>Canada (Fair)</td>
<td>British Columbia Linked Health Dataset (BCLHD)</td>
<td>January 1, 1990 and December 31, 1996</td>
<td>NR</td>
<td>Methylphenidate (mean dose NR)</td>
</tr>
</tbody>
</table>
## Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Concomitant medication</th>
<th>Safety Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Screened</th>
<th>Eligible</th>
<th>Enrolled</th>
<th>Withdrawn</th>
<th>Lost to fu</th>
<th>Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brehaut</td>
<td>2003</td>
<td>Canada (Fair)</td>
<td>Any individual who was &lt;19 years of age on December 31, 1996. Children were included in the childhood behavior disorder (CBD) group if they were listed as having been prescribed MPH at least once between January 1, 1990 and December 31, 1996. All other children and youth were included in the no CBD group.</td>
<td>51.4% male 51.4% female</td>
<td>&lt;4 y=18.2% 4-8, 11 mo=27.2% 9-13 y, 11 mo=27.4% 14-18 y, 11 mo=27.1%</td>
<td>1,028,028 exposed</td>
<td>Eligible NR</td>
<td>Selected=1,026,873</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Safety Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brehaut</td>
<td>2003</td>
<td>Canada</td>
<td>Elementary School Children - Methylphenidate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Injury</th>
<th>No CBD Frequencies (n=1,010,067)</th>
<th>CBD Frequencies (n=16,806)</th>
<th>Odds Ratios 99% CI</th>
<th>Logistic Regression Odds Ratios 99% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature of injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractures</td>
<td>20,025 (2.0%)</td>
<td>723 (4.3%)</td>
<td>2.22</td>
<td>1.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.01-2.46</td>
<td>1.27-1.58</td>
</tr>
<tr>
<td>Open wounds</td>
<td>4858 (0.5%)</td>
<td>224 (1.3%)</td>
<td>2.80</td>
<td>1.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.34-3.34</td>
<td>1.56-2.29</td>
</tr>
<tr>
<td>Poisoning/toxic effect</td>
<td>3882 (0.4%)</td>
<td>184 (1.1%)</td>
<td>2.87</td>
<td>2.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.36-3.49</td>
<td>2.16-3.30</td>
</tr>
<tr>
<td>Intracranial</td>
<td>2675 (0.3%)</td>
<td>107 (0.6%)</td>
<td>2.41</td>
<td>1.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.87-3.11</td>
<td>1.27-2.19</td>
</tr>
<tr>
<td>Concussion</td>
<td>2667 (0.3%)</td>
<td>127 (0.8%)</td>
<td>2.88</td>
<td>1.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.27-3.64</td>
<td>1.42-2.35</td>
</tr>
<tr>
<td>Burns</td>
<td>1301 (0.1%)</td>
<td>45 (0.3%)</td>
<td>2.08</td>
<td>1.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.41-3.08</td>
<td>1.31-3.02</td>
</tr>
<tr>
<td>Total</td>
<td>32,242 (3.2%)</td>
<td>1,257 (7.5%)</td>
<td>2.45</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.27-2.65</td>
<td>1.54-1.81</td>
</tr>
<tr>
<td>Cause of injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falls</td>
<td>16426 (1.6%)</td>
<td>573 (3.4%)</td>
<td>2.14</td>
<td>1.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.91-2.39</td>
<td>1.29-1.64</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>6166 (0.6%)</td>
<td>168 (1.0%)</td>
<td>1.64</td>
<td>1.37</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.34-2.01</td>
<td>1.10-1.71</td>
</tr>
<tr>
<td>Struck by object</td>
<td>4146 (0.4%)</td>
<td>157 (0.9%)</td>
<td>2.29</td>
<td>1.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.85-2.82</td>
<td>1.07-1.69</td>
</tr>
<tr>
<td>Motor vehicle accident</td>
<td>3333 (0.3%)</td>
<td>136 (0.8%)</td>
<td>2.46</td>
<td>1.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.97-3.09</td>
<td>1.23-1.99</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>2370 (0.2%)</td>
<td>87 (0.5%)</td>
<td>2.21</td>
<td>2.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.67-2.93</td>
<td>1.58-2.85</td>
</tr>
<tr>
<td>Nonmotor vehicle pedal</td>
<td>2360 (0.2%)</td>
<td>118 (0.7%)</td>
<td>3.02</td>
<td>2.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.37-3.85</td>
<td>1.33-2.22</td>
</tr>
<tr>
<td>Suffocation</td>
<td>813 (0.1%)</td>
<td>23 (0.1%)</td>
<td>1.70</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.99-2.93</td>
<td>0.59-5.17</td>
</tr>
<tr>
<td>Drowning</td>
<td>185 (&lt;0.1%)</td>
<td>6 (&lt;0.1%)</td>
<td>1.95</td>
<td>1.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.67-5.68</td>
<td>0.59-5.17</td>
</tr>
<tr>
<td>Total</td>
<td>33855 (3.4%)</td>
<td>1180 (7.0%)</td>
<td>2.18</td>
<td>1.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.01-2.36</td>
<td>1.40-1.66</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Design</td>
<td>Eligibility Criteria</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>--------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Gadow</td>
<td>1999</td>
<td>U.S. (Fair)</td>
<td>Long-term follow-up to participation in an 8-233k controlled trial of methylphenidate and placebo Setting: NR Noncomparative</td>
<td>DSM-III-R diagnostic criteria for ADHD and either chronic motor tic disorder and, in general, were above cutoff on 2 of 3 parent-completed and 2 of 3 teacher-completed</td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Concomitant medication</th>
<th>Safety Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Screened</th>
<th>Eligible</th>
<th>Enrolled</th>
<th>Withdrawn</th>
<th>Lost to fu</th>
<th>Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadow</td>
<td>1999</td>
<td>NR</td>
<td>Height</td>
<td>Short-term dose trial (n=34)</td>
<td>NR/NR/34</td>
<td>Number of subjects at each follow-up visit/number receiving stimulants: 6 months=28/27 12 months=33/30 18 months=29/26 24 months=29/26 (1 switched to dextroamphetamine)</td>
<td>91.2% male</td>
<td>Race NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S.</td>
<td>(Fair)</td>
<td>NR</td>
<td>Weight</td>
<td>Mean age=8.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Screened:**
- Number of subjects at each follow-up visit/number receiving stimulants:
  - 6 months=28/27
  - 12 months=33/30
  - 18 months=29/26
  - 24 months=29/26 (1 switched to dextroamphetamine)

**Withdrawn:**
- Number of subjects at each follow-up visit/number receiving stimulants:
  - 6 months=28/27
  - 12 months=33/30
  - 18 months=29/26
  - 24 months=29/26 (1 switched to dextroamphetamine)
**Evidence Table 15. Observational Studies - Long-term Safety**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Safety Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gadow</td>
<td>1999</td>
<td>U.S. (Fair)</td>
<td>Weight in kg (mean expected/actual/difference/p-value): 41.95/41.23/0.72/p=0.59</td>
<td>Only 2 comparisons indicated that tics were worse on medication than placebo (data nr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Height in cm (mean expected/actual/difference/p-value): 147.48/146.81/0.67/p=0.57</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tic measurements (diagnostic/placebo/6 month/12 month/18 month/24 month)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>YGTSS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total Motor Tics: 13.9/11.4/12.1/12.2/13.0/12.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total Phonic Tics: 11.2/7.9/7.6/8.1/8.3/8.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Global Severity Scale: 42.9/26.5/27.1/30.0/31.3/29.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>STESS: 2.9/1.6/1.8/2.0/1.9/1.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TS-CGI: 2.6/3.1/3.1/2.3/2.4/2.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TS unified Rating Scale:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Shapiro Symptom Checklist</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No of Motor Tics: 13.2/11.7/12.0/12.8/14.0/13.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. of Vocal Tics: 5.0/3.1/2.5/2.9/2.8/2.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2-Minute Tic Count</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Motor Tic Count: 10.0/9.5/13.8/14.4/18.1/17.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vocal Tic Count: 1.1/0.6/0.4/1.1/1.3/1.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GTRS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Motor Tic Index: 4.8/4.9/5.0/5.0/4.8/4.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vocal Tic Index: 1.9/1.0/1.1/1.1/1.4/1.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tic Severity Index: 3.2/1.4/1.8/2.2/2.5/2.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LeWitt Disability Scale: 61.9/68.6/72.9/72.4/70.7/73.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CGI-OC: 2.7/1.6/1.8/1.7/1.9/1.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parent Ratings</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GTRS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Motor Tic Index: 3.7/2.2/2.4/3.2/2.5/2.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vocal Tic Index: 1.8/0.9/0.9/1.2/0.8/0.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tic Severity Index: 3.3/1.6/1.8/2.4/1.9/2.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Classroom observations:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Motor Tic Frequency: 18.6/18.6/23.8/21.0/21.0/19.5/18.9</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Design</td>
<td>Eligibility Criteria</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Quinn</td>
<td>1975</td>
<td>U.S.</td>
<td>Unblinded follow-up of samples that continued their original randomly assigned medication (6-week, randomized, DB study: Rapoport, 1974)</td>
<td>NR</td>
</tr>
</tbody>
</table>
## Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Concomitant medication</th>
<th>Safety Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Screened</th>
<th>Eligible</th>
<th>Enrolled</th>
<th>Withdrawn</th>
<th>Lost to fu</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinn</td>
<td>1975</td>
<td>NR</td>
<td>Height</td>
<td>Mean age nr</td>
<td>100% male</td>
<td>Race NR</td>
<td>NR/NR/75</td>
<td>28 (37.3%) withdrawn</td>
<td>overall/lost to fu=0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S. (Fair)</td>
<td></td>
<td></td>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Safety Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinn</td>
<td>1975</td>
<td>U.S. (Fair)</td>
<td>Safety compared only for children initially assigned to the active drug group and continued on the same medication for one year (methylphenidate n=23; imipramine n=13)</td>
<td>Anorexia: 9 (47%) vs 5 (39%) Seizures: none reported</td>
</tr>
</tbody>
</table>

Condition 1 = Imipramine
Condition 2 = methylphenidate all doses (n=23)
Condition 3 = methylphenidate > 20 mg a day (n=5)
Condition 4 = methylphenidate 20 mg a day or less (n=18)
Condition 5 = no treatment (n=12)

Weight change (percentile scores): -7.54 vs -8.81 vs -15.40 vs -6.88 vs +1.61

t-scores, p-values for comparisons of condition 5 with 1; 2; 3; 4: 2.45, p<0.01; 3.42, p<0.005; 4.18, p<0.005; 3.44, p<0.005

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
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Eligibility Criteria</th>
<th>Duration</th>
<th>Interventions (mean dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattes</td>
<td>1983</td>
<td>U.S.</td>
<td>Before-after (open trial of methylphenidate)</td>
<td>Children had to be considered hyperactive both in school and at either home or the clinic; furthermore, a high level of disruptive behavior was required</td>
<td>Up to 4 years</td>
<td>Methylphenidate mean dosages (mg): Up to 1 year: 39.9 1-2 year: 41.3 2-3 year: 41.0 3-4 year: 41.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td>Setting: NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Noncomparative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Concomitant medication</td>
<td>Safety Assessment</td>
<td>Age</td>
<td>Gender</td>
<td>Ethnicity</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>------------------------</td>
<td>------------------</td>
<td>-----</td>
<td>--------</td>
<td>-----------</td>
</tr>
<tr>
<td>Mattes</td>
<td>1983</td>
<td>Thioridazine hydrochloride received by 34 (39.5%) at some time during the study</td>
<td>Changes in weight and height percentiles</td>
<td>Mean age NR</td>
<td>Gender NR</td>
<td>Race NR</td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Safety Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattes</td>
<td>1983</td>
<td>U.S. (Fair)</td>
<td></td>
<td>Once a year the methylphenidate regimen was replaced by a single-blind placebo trial. Only children whose behavior clearly deteriorated while they received placebo were returned to active treatment. Many of the children discontinued the medication regimen during the summer; methylphenidate therapy was reinstated in the fall only if behavioral complaints from school were received.</td>
</tr>
</tbody>
</table>

#### Height

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Pretreatment</th>
<th>End of year</th>
<th>t</th>
<th>p</th>
<th>Correlation with treatment duration (Pearson’s r, p-value)</th>
<th>Correlation with mean daily dose (Pearson’s r, p-value)</th>
<th>Correlation with total cumulative dose (Pearson’s r, p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51</td>
<td>51.1</td>
<td>49.7</td>
<td>1.56</td>
<td>NS</td>
<td>-.20, NS</td>
<td>0.04, NS</td>
<td>-0.17, NS</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>51.7</td>
<td>43.6</td>
<td>7.10</td>
<td>&lt;0.001</td>
<td>0.18, NS</td>
<td>0.09, NS</td>
<td>0.16, NS</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>60.5</td>
<td>47.1</td>
<td>8.13</td>
<td>&lt;0.001</td>
<td>0.04, NS</td>
<td>0.29, NS</td>
<td>0.24, NS</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>66.6</td>
<td>48.5</td>
<td>6.50</td>
<td>&lt;0.001</td>
<td>0.33, NS</td>
<td>0.15, NS</td>
<td>0.28, NS</td>
</tr>
</tbody>
</table>

#### Weight

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Pretreatment</th>
<th>End of year</th>
<th>t</th>
<th>p</th>
<th>Correlation with treatment duration (Pearson’s r, p-value)</th>
<th>Correlation with mean daily dose (Pearson’s r, p-value)</th>
<th>Correlation with total cumulative dose (Pearson’s r, p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>59.2</td>
<td>49.5</td>
<td>6.81</td>
<td>&lt;0.001</td>
<td>0.17, NS</td>
<td>0.17, NS</td>
<td>0.26, p&lt;0.05</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>57.4</td>
<td>41.5</td>
<td>9.24</td>
<td>&lt;0.001</td>
<td>0.31, p&lt;0.01</td>
<td>0.12, NS</td>
<td>0.29, p&lt;0.05</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>62.1</td>
<td>43.5</td>
<td>10.18</td>
<td>&lt;0.001</td>
<td>0.05, NS</td>
<td>0.05, NS</td>
<td>0.09, NS</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>62.5</td>
<td>41.9</td>
<td>5.82</td>
<td>&lt;0.001</td>
<td>0.39, p&lt;0.05</td>
<td>-0.01, NS</td>
<td>0.018, NS</td>
</tr>
</tbody>
</table>

Multiple regression analysis of relationship of dosage and final height (n=42, includes 6 children who were off MPH at 3 years)

<table>
<thead>
<tr>
<th>Step</th>
<th>Factors</th>
<th>Multiple correlation</th>
<th>Total explained variance (%)</th>
<th>Unique variance contribution of each factor (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baseline height</td>
<td>0.94</td>
<td>87.8</td>
<td>87.8 (Pearson’s r)</td>
</tr>
<tr>
<td>2</td>
<td>Baseline weight</td>
<td>0.94</td>
<td>88.2</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>Age at final height measurement</td>
<td>0.94</td>
<td>88.3</td>
<td>0.0</td>
</tr>
<tr>
<td>4</td>
<td>Baseline age</td>
<td>0.94</td>
<td>88.5</td>
<td>0.2</td>
</tr>
<tr>
<td>5</td>
<td>Total cumulative dosage of MPH</td>
<td>0.95</td>
<td>90.5</td>
<td>2.0 (p&lt;0.01)</td>
</tr>
</tbody>
</table>
## Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Eligibility Criteria</th>
<th>Duration</th>
<th>Interventions (mean dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wernicke</td>
<td>2003</td>
<td>U.S.</td>
<td>Pooled analyses of (1) 3 short-term trials in children/adolescents</td>
<td>Children and adolescents with ADHD</td>
<td>At least 1 year</td>
<td>Atomoxetine maximum dosage of 2 mg/kg/day administered in two divided doses (mean dose nr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td>(Spencer 2002, Michelson 2001); (2) 2 short-term trials in adults</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Michelson 2003); and (3) long-term, open-label extensions or a blinded continuation following the three short-term treatment trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The short-term QTc-interval and cardiovascular adverse events data were not reported in the original publications.
## Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Concomitant medication</th>
<th>Safety Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wernicke</td>
<td>2003</td>
<td>U.S.</td>
<td>NR</td>
<td>QT interval prolongation using Bazett (exponent of 0.5) and Fridericia (exponent of 0.33) corrections. Categorical changes (increases of at least 30, 60, or to at least 500 msec) are those proposed by the European CPMP</td>
<td>Children/adolescents (n=550)</td>
<td>Mean age=10.5</td>
<td>75.1% male 78.5% white</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td></td>
<td></td>
<td>Adults</td>
<td>Mean age=41.1</td>
<td>64.9% male 90.8% white</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Long-term population data nr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Safety Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wernicke</td>
<td>2003</td>
<td>U.S.</td>
<td>Baseline and change in corrected (Fridericia formula) QT intervals: short-term treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### QTcD
- **Mean change at endpoint**
  - Atomoxetine: -3.1, p-value: NS
  - Placebo: -4.4, p-value: NS
- **Increase ≥ 30 msec [no. (%)]**
  - Atomoxetine: 7 (2.2%), p-value: NS
  - Placebo: 9 (4.5%), p-value: NS
- **Increase ≥ 60 msec or ≥ 500 msec:** None for children/adolescents or adults

#### QTcB
- **Mean change at endpoint**
  - Atomoxetine: +1.5, p-value: 0.004
  - Placebo: -4.5, p-value: NS
- **Increase ≥ 30 msec [no. (%)]**
  - Atomoxetine: 20 (6.2%), p-value: 0.004
  - Placebo: 15 (7.4%), p-value: NS
- **Increase ≥ 60 msec [no. (%)]**
  - Atomoxetine: 1 (0.3%), p-value: NS
  - Placebo: 2 (1.0%), p-value: NS
- **Increase ≥ 500 msec:** None for children/adolescents or adults

#### QTcF
- **Mean change at endpoint**
  - Atomoxetine: -5.3, p-value: NS
  - Placebo: -4.4, p-value: NS
- **Increase ≥ 30 msec [no. (%)]**
  - Atomoxetine: 6 (1.8%), p-value: NS
  - Placebo: 5 (2.5%), p-value: NS
- **Increase ≥ 60 msec or ≥ 500 msec:** None for children/adolescents or adults

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

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

<table>
<thead>
<tr>
<th></th>
<th>Children/adolescents</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitations</td>
<td>Atomoxetine (n=340)</td>
<td>Placebo (n=207)</td>
</tr>
<tr>
<td></td>
<td>1 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Atomoxetine (n=269)</td>
<td>Placebo (n=263)</td>
</tr>
<tr>
<td></td>
<td>10 (3.7%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>4 (1.5%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td></td>
<td>1 (0.4%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Pharmacologic Treatments for ADHD Page 585 of 616**
## Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Design</th>
<th>Eligibility Criteria</th>
<th>Duration</th>
<th>Interventions (mean dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross</td>
<td>1976</td>
<td>Retrospective analysis of height and weight data among 100 children treated for at least 2 years for ADHD, and with mean follow-up of 6 years. Setting: NR Comparative</td>
<td>Subjects received at least 2 (mean=5) years of treatment. Mean follow-up time: 5.8 years for MPH, 6.8 years for dextroamphetamine.</td>
<td>Methylphenidate mean dose 34 mg/day, n=60 Dextroamphetamine mean dose 16.5 mg/day, n=24 (Imipramine/desipramine, n=16)</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Concomitant medication</td>
<td>Safety Assessment</td>
<td>Age</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>------------------------</td>
<td>-------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Gross</td>
<td>1976</td>
<td>U.S. (Fair)</td>
<td>NR</td>
<td>Changes in weight and height percentiles, compared with Iowa city norms</td>
<td>Mean age at onset of treatment: 9</td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Safety Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross 1976</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Methylphenidate group: changes in percentiles of weight and height</td>
<td>Loss of weight compared with expected norms occurs during the first 3 years with MPH and dextroamphetamine, but there is a statistically significant increase in weight and height percentiles at final measurement in both treatment groups. Compliance was assessed by checking prescription records.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time after onset (yrs)</th>
<th>N on medication</th>
<th>Mean daily dose</th>
<th>Average change in percentile (p-value)</th>
<th>Weight</th>
<th>Height</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>24.4</td>
<td>-5.2 (p&lt;0.05)</td>
<td>-0.1 (ns)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>31.7</td>
<td>-4.3 (ns)</td>
<td>+0.4 (ns)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>38.5</td>
<td>-3.0 (ns)</td>
<td>-1.9 (ns)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>43.3</td>
<td>+7.5 (ns)</td>
<td>+7.0 (ns)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>47.2</td>
<td>+7.2 (ns)</td>
<td>+7.1 (ns)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>51.2</td>
<td>+10.4 (ns)</td>
<td>+8.9 (ns)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>40.0</td>
<td>+24.4 (p&lt;0.05)</td>
<td>+14.9 (p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>40.0</td>
<td>+19.1 (p&lt;0.05)</td>
<td>+12.2 (p&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>At final f/u (mean 5.8y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>43.8</td>
<td>+11.4 (p&lt;0.001)</td>
<td>+12.8 (p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Dextroamphetamine group: changes in percentiles of weight and height</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24</td>
<td>12.2</td>
<td>-5.9 (p&lt;0.05)</td>
<td>-1.8 (ns)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>14.5</td>
<td>-6.0 (ns)</td>
<td>+0.8 (ns)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>17.7</td>
<td>-3.4 (ns)</td>
<td>+1.9 (ns)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>18.9</td>
<td>+2.2 (ns)</td>
<td>+5.2 (ns)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>20.1</td>
<td>+3.2 (ns)</td>
<td>+6.2 (ns)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>16.7</td>
<td>+9.3 (ns)</td>
<td>+9.8 (ns)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>18.0</td>
<td>+18.1 (ns)</td>
<td>+13.4 (ns)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>20.0</td>
<td>+10.5 (ns)</td>
<td>+13.2 (ns)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>25.0</td>
<td>+41.0 (ns)</td>
<td>+17.3 (ns)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>At final f/u (mean 6.8y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>19.6</td>
<td>+16.0 (p&lt;0.02)</td>
<td>+10.9 (p&lt;0.01)</td>
<td></td>
</tr>
</tbody>
</table>

Patients who had discontinued medication at final follow-up had larger increments in percentiles for both height and weight compared with patients still taking medication, but differences were not significant. Analysis by age at treatment onset found that older children made greater gains in weight and height percentiles than younger children, but the difference was not statistically significant. Correlations between mean dose during treatment vs. change in percentile from onset to final follow-up, and between age at onset of treatment vs. change in percentile from onset to final follow-up, were low in magnitude (0.03 to –0.22 for r) and not significant.
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Eligibility Criteria</th>
<th>Duration</th>
<th>Interventions (mean dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safer</td>
<td>1972</td>
<td>U.S. (Fair)</td>
<td>Retrospective analysis of height and weight data among 2 groups: 1) hyperactive children who had been on stimulant medication for 9 months and had been either kept on or taken off treatment during the 3-month summer period; 2) hyperactive children, some who received continuous medication for 2+ years, and some who received no medication. Setting: NR Comparative</td>
<td>Group 1: 20 hyperactive children in an elementary school who were known by the school nurse to be regularly taking either methylphenidate or dextroamphetamine for hyperactivity. Group 2: 9 hyperactive children who had been on medication continuously for 2 or more years, and 7 children who although referred for stimulants were not given any owing to parental objection.</td>
<td>Group 1: 1 year Group 2: 2+ years</td>
<td>Group 1: Methylphenidate 28.7 mg/day Dextroamphetamine 11.8 mg/day Group 2: Methylphenidate continuous treatment for 2+ years (dose not reported; 7 of 9 subjects were also in group 1 above) Control group: no medication</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Concomitant medication</td>
<td>Safety Assessment</td>
<td>Age Gender Ethnicity</td>
<td>Screened Eligible Enrolled</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>----------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Safer</td>
<td>1972</td>
<td>U.S.</td>
<td>NR</td>
<td>Group 1: Height and weight were recorded in September, 1970 at the beginning of the school year, June 1971 before summer vacation, and again in September 1971.</td>
<td>Group 1: Mean age 9.8 Gender NR 100% white</td>
<td>NR/NR/29: 20 in Group 1, 16 in Group 2, with 7 occurring in both groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td></td>
<td>Group 2: The nurse obtained past height and weight measurements from school admission information at the age of five or six.</td>
<td>Group 2: Mean age NR Gender NR Ethnicity NR</td>
<td></td>
</tr>
</tbody>
</table>
So far, their efforts have included 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.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Safety Outcomes</th>
<th>Weight gain in school year (Sept-June), kg/mo</th>
<th>Weight gain in summer (June-July-Aug), kg/mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAFER</td>
<td>1972</td>
<td>U.S. (Fair)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>N</td>
<td>Dose of MPH mg/day</td>
<td>Dose of DAMP mg/day</td>
<td>Weight gain in school year (Sept-June), kg/mo</td>
<td>Weight gain in summer (June-July-Aug), kg/mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All patients</td>
<td>All on MPH vs all</td>
<td>All patients</td>
<td>Patients on MPH</td>
</tr>
<tr>
<td>Continued meds. in summer</td>
<td>7</td>
<td>37.5</td>
<td>11.7</td>
<td>0.15</td>
<td>0.23 vs 0.12 (p&lt;0.05)</td>
</tr>
<tr>
<td>Discontinued meds. in summer</td>
<td>13</td>
<td>24.0</td>
<td>11.8</td>
<td>0.17</td>
<td>0.45 (130% of expected gain)</td>
</tr>
<tr>
<td>P-value, Continued vs Discontinued</td>
<td>p&lt;0.05</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Group 2</td>
<td>N</td>
<td>Average percentile changes in growth over 2 or more years</td>
<td>Weight</td>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Medication 2+ years</td>
<td>9</td>
<td>-17.5</td>
<td>-16.3</td>
<td>Mean yearly weight gain of children on stimulants for 2 years was 1.8 kg. Compared with expected gain of 3.1 kg, mean percentile for weight decreased from 62nd to 40th.</td>
<td></td>
</tr>
<tr>
<td>No medication</td>
<td>7</td>
<td>+1.3</td>
<td>+4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value, Medicated vs. Not</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Eligibility Criteria</th>
<th>Duration</th>
<th>Interventions (mean dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satterfield</td>
<td>1979</td>
<td>U.S.</td>
<td>Prospective study of weight and height in boys treated for two years with methylphenidate. Setting: clinic, single-site Noncomparative</td>
<td>Subjects were all children who were referred to Gateways Hospital Hyperkinetic Children's Clinic, Los Angeles, from September 1973 thru December 1974, and met the following criteria: boys aged 6-12, attending school, having normal vision and hearing, of normal intelligence on the Wechsler Intelligence Scale for Children (80+); hyperactive by behavioral criteria that required evidence of chronic symptoms of hyperexcitability, impulsivity, and poor attention span, as reported by parents and teachers; nonpsychotic, non-brain-damaged. 20% of subjects had received stimulant drugs prior to entering the study.</td>
<td>2 years</td>
<td>Methylphenidate, taken bid (morning and noon) on 5 weekdays; some patients required a third dose midafternoon, and others required medication 7 days/week. Some children took the medication only during the school year; others continued medication during the summer but at a lower dosage.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Good)</td>
<td></td>
<td></td>
<td></td>
<td>Mean dose, year 1: 24.2 mg/day, 0.47 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean dose, year 2: 0.59 mg/kg/day</td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Concomitant medication</th>
<th>Safety Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satterfield</td>
<td>1979</td>
<td>NR</td>
<td>Initial height and weight measures were converted to percentile rank based on the Iowa growth tables for normal children. Using these tables, this percentile rank predicted height and weight at years 1 and 2 for each subject. Expected gains for years 1 and 2 were computed based on initial and predicted percentiles. Growth deficits were computed from predicted vs observed growth. Monthly weight and height measurements were obtained by research staff on a pediatric scale, with child's shoes removed and pockets emptied. All measurements were used to determine growth rates and total year's growth.</td>
<td>Age range 6-12, mean age NR 100% male Ethnicity NR</td>
<td>NR/NR/72</td>
<td>NR/NR/72</td>
</tr>
<tr>
<td>(Good)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Final Report Drug Effectiveness Review Project
## Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Safety Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satterfield</td>
<td>1979</td>
<td>U.S. (Good)</td>
<td></td>
<td>Adherence in 93% of patients was confirmed by monthly urinalysis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Significant deficits in growth were observed in the 1st year.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Greater-than-expected gains in height and weight occurred in the 2nd year of treatment, though these increases were not statistically significant.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Total</th>
<th>72</th>
<th>0.47</th>
<th>-29% (p&lt;0.01)</th>
<th>0.85 kg less</th>
<th>-19% (p&lt;0.001)</th>
<th>1.03 cm less</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Received summer med.</td>
<td>31</td>
<td>0.627</td>
<td>-35% (p&lt;0.05)</td>
<td>-17% (p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No summer medication</td>
<td>41</td>
<td>0.37</td>
<td>-24.5% (p&lt;0.05)</td>
<td>-19.5% (p&lt;0.05)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year 2</th>
<th>Total</th>
<th>48</th>
<th>0.59</th>
<th>-10% (ns)</th>
<th>0.31 kg less</th>
<th>+8% (ns)</th>
<th>0.42 cm more</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Received summer med.</td>
<td>24</td>
<td>0.81</td>
<td>-20% (p&lt;0.05)</td>
<td>0.67 kg less</td>
<td>+7.5% (ns)</td>
<td>0.36 cm more</td>
</tr>
<tr>
<td></td>
<td>No summer medication</td>
<td>24</td>
<td>0.37</td>
<td>+2.5% (ns)</td>
<td>0.25 kg more</td>
<td>+10% (ns)</td>
<td>0.49 cm more</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accumulated growth: Year 1 plus Year 2</th>
<th>Total</th>
<th>48</th>
<th>0.56</th>
<th>-13% (ns)</th>
<th>+2% (ns)</th>
</tr>
</thead>
</table>

Height and weight deficits in year 1 and in year 2 were not significantly correlated with average daily dosage, age, or before-treatment height or weight. Height and weight deficits in the first year were not significantly correlated with similar deficits in the second year of treatment.
## Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Eligibility Criteria</th>
<th>Duration</th>
<th>Interventions (mean dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McNutt</td>
<td>1976a (preliminary report)</td>
<td>U.S.</td>
<td>Long-term follow-up anterospective study of subjects in short-term studies on the effects of different doses of methylphenidate</td>
<td>Hyperactive children on methylphenidate that had been subjects in short-term studies</td>
<td>≥ 8 months of medication during a 12-month period</td>
<td>Methylphenidate mean daily doses: 12-month cohort: 24.1 mg 24-month cohort: 29.1 mg</td>
</tr>
<tr>
<td>McNutt</td>
<td>1976b</td>
<td>U.S.</td>
<td></td>
<td></td>
<td>≥ 16 months of medication during a 24-month period</td>
<td>Dosing schedule NR</td>
</tr>
<tr>
<td></td>
<td>(Fair)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Concomitant medication</td>
<td>Safety Assessment</td>
<td>Age</td>
<td>Gender</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------</td>
<td>---------</td>
<td>------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>--------</td>
</tr>
<tr>
<td>McNutt 1976a</td>
<td>McNutt 1976b</td>
<td>U.S.</td>
<td>NR</td>
<td>Height: measured with a stadiometer and recorded in cm to the nearest mm; taken while the subject was standing with heels together with the body help in a maximally erect position and hands on the hips with a maximal inspiration of air.</td>
<td>Medicated (n=28) vs nonmedicated (n=24) vs control (n=47) vs overall</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(preliminary report)</td>
<td></td>
<td></td>
<td></td>
<td>12-month</td>
<td>Mean age: 10.5 vs 10.7 vs 9.71 vs 10.2 vs 85.7% vs 87.5% vs 68% vs 77.8% Race nr</td>
</tr>
<tr>
<td></td>
<td>McNutt 1976b</td>
<td>U.S.</td>
<td>(Fair)</td>
<td>Weight: after urine was voided, measured with the subject standing on a platform scale (Howe-Richardson) attired in standard lightweight gym shorts and barefooted; determined to the nearest grams.</td>
<td>24-month</td>
<td>Mean age: 10.1 vs 9.7 vs 9.87 vs 9.9 vs 84.6% vs 90% vs 85.7% vs 86.5% Race nr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Body composition: subcutaneous fat, body girth, and skeletal width were all made on the right side of the body; body fat and lean body mass were estimated from body weight and upper arm and back skinfold thicknesses according to regression equations established by Lohman; two thicknesses of skin and subcutaneous fat were included; reading from the calipers were recorded to the nearest mm and the mean of 3 readings at each site was rounded to the nearest 0.1 mm and used as the representative reading</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Safety Outcomes</td>
<td>Comments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------</td>
<td>---------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McNutt 1976a</td>
<td>(preliminary report)</td>
<td>U.S. (Fair)</td>
<td>12 months Growth (age, height, and weight): medicated=controls (data nr); Analysis of covariance (with age as covariate): medicated=controls (data nr); medicated=nonmedicated Lean body mass, percent body fat, body girth: medicated=controls; Analysis of covariance (with age as covariate): medicated=controls (data nr); medicated=nonmedicated Skeletal width: hyperactives&gt;controls, F(1.73)=4.75, p&lt;0.03; Analysis of covariance (with age as covariate): hyperactives=controls</td>
<td>Significant difference in age between medicated and controls, F(1.73)=5.83, p&lt;0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McNutt 1976b</td>
<td>U.S. (Fair)</td>
<td></td>
<td>24 months Growth: medicated=controls; medicated=nonmedicated Body composition: medicated=controls, but group-by-time interaction on percent body fat (hyperactives increased, controls decreased); medicated=nonmedicated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Design</td>
<td>Eligibility Criteria</td>
<td>Duration</td>
<td>Interventions (mean dose)</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>--------</td>
<td>----------------------</td>
<td>----------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Wilens</td>
<td>2003</td>
<td>U.S. (Fair)</td>
<td>Open-label trial of OROS MPH, non-randomized, 12-month study in children who had used OROS MPH in previous trials and were found to be responders. Setting: 14 sites Non-comparative</td>
<td>All subjects except one had participated in a previous trial of OROS MPH. Eligible for inclusion were children with ADHD, aged 6-13, with normal urinalysis, hematology, and blood chemistry. Subjects who were already receiving specific behavioral interventions for ADHD on an ongoing basis were permitted to enter the study, but new behavioral interventions could not be initiated during the study. Children with mild or moderate vocal or motor tics, but not a diagnosis of Tourette's syndrome, were included. Exclusions: children with Tourette's syndrome; an ongoing seizure disorder; a psychotic disorder; clinically significant GI problems: a history of hypertension; known hypersensitivity to MPH; a coexisting condition or concurrent medication likely to interfere with MPH; females who had reached menarche.</td>
<td>12 months</td>
<td>Methylphenidate in a once-daily, osmotic controlled-release formulation (OROS MPH) Subjects were assigned to one of 3 dosing levels of OROS MPH (18 mg, 36 mg, or 54 mg qd) based on previous treatment. Dose could be adjusted up or down in 18 mg increments during the monthly clinic visits. Doses could be reduced or discontinued on weekends or nonschool days, or on other medication holidays. Mean dose at study entry: 35 mg/day Mean dose at 12 months: 41 mg/day</td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Concomitant medication</th>
<th>Safety Assessment</th>
<th>Age</th>
<th>Screened</th>
<th>Eligible</th>
<th>Enrolled</th>
<th>Withdrawn</th>
<th>Lost to fu</th>
<th>Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilens</td>
<td>2003</td>
<td>U.S. (Fair)</td>
<td>Allowed, but not specified</td>
<td>Urinalysis, hematology, serum chemistry were performed at baseline, at 6 and 12 months. Height, weight, blood pressure, and pulse were recorded at monthly clinic visits. Adverse events were elicited by the investigator and by spontaneous report by the subjects or their parents caregivers, and assessed as to severity and possible relationship to study medication. At monthly visits, parents were asked about their child's sleep quality; whether their child had experienced tics, or whether tics had changed in severity or specificity in the previous month.</td>
<td>Mean age 9.2</td>
<td>NR/NR/436</td>
<td>143 (32.8%)</td>
<td>withdrew, 25 because data from one site was found to be unreliable</td>
<td>16 (3.7%)</td>
<td>lost to fu</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>83% male</td>
<td></td>
<td></td>
<td></td>
<td>407 (93.3%)</td>
<td>analyzed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>86% white</td>
<td></td>
<td></td>
<td></td>
<td>28 (6.4%)</td>
<td>withdrew due to AEs</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Safety Outcomes</td>
<td>N (%)</td>
<td>Withdrawals due to AE</td>
<td>Specific adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>-----------------</td>
<td>-------</td>
<td>-----------------------</td>
<td>------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilens</td>
<td>2003</td>
<td>U.S. (Fair)</td>
<td>Headache</td>
<td>102 (25.1)</td>
<td>1</td>
<td>Tics: New onset occurred in 23 (6.4%) of 359 subjects with no known history of tics.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Insomnia</td>
<td>60 (14.7)</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Appetite suppression</td>
<td>55 (13.5)</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abdominal pain</td>
<td>31 (7.6)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Twitching</td>
<td>31 (7.6)</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Aggravation reaction</td>
<td>10 (2.5)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Somnolence</td>
<td>10 (2.5)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reaction unevaluable</td>
<td>9 (2.2)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiety</td>
<td>9 (2.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight loss</td>
<td>8 (2.0)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emotional lability</td>
<td>8 (2.0)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hostility</td>
<td>8 (2.0)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nausea</td>
<td>7 (1.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dizziness</td>
<td>7 (1.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vomiting</td>
<td>6 (1.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nervousness</td>
<td>6 (1.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Depression</td>
<td>6 (1.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Asthenia</td>
<td>5 (1.2)</td>
<td></td>
<td>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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypertension</td>
<td>5 (1.2)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Apathy</td>
<td>4 (1.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Worsening of ADHD</td>
<td>NR</td>
<td>3</td>
<td>Growth: Mean weight decreased by 0.1 kg over the first 3 months then increased over the remainder of the study. See table below.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Compulsive skin picking</td>
<td>NR</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hallucinations</td>
<td>NR</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Growth Baseline</td>
<td>34.2</td>
<td>Month 3</td>
<td>34.1</td>
<td>Month 6</td>
<td>34.5</td>
<td>Month 9</td>
<td>35.6</td>
<td>Month 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Height (cm)</td>
<td>137.1</td>
<td>138.4</td>
<td>139.6</td>
<td>140.8</td>
<td>142.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rate of change (cm/mo)</td>
<td>---</td>
<td>+0.43</td>
<td>+0.40</td>
<td>+0.40</td>
<td>+0.50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Weight (kg)</td>
<td>---</td>
<td>-0.033</td>
<td>+0.133</td>
<td>+0.366</td>
<td>+0.400</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rate of change (kg/mo)</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypertension</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Apathy</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Worsening of ADHD</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Compulsive skin picking</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hallucinations</td>
<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Most children were already MPH responders prior to entry into the study, and patients with known hypersensitivity to MPH were excluded.
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Design</th>
<th>Eligibility Criteria</th>
<th>Duration</th>
<th>Interventions (mean dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gualtieri</td>
<td>1985</td>
<td>U.S. (Fair)</td>
<td>Open-label 3-6 month followup of MPH responders.</td>
<td>Subjects (n=8) who appeared to respond favorably to MPH in either a short-term efficacy study or in open clinical trials. All subjects (n=8) had initially responded with improvement in attention span, greater work efficiency, decreased feelings of restlessness and impatience, improved interpersonal relationships, and diminished temper outbursts. Two of these subjects were also narcoleptics, and in both cases MPH also led to control of sleep attacks.</td>
<td>3-6 months</td>
<td>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.</td>
</tr>
<tr>
<td>Millichap</td>
<td>1977</td>
<td>U.S. (Fair)</td>
<td>Before-after Setting: Children's Memorial Hospital (Chicago)</td>
<td>Boys, 5 to 10 years of age, referred for pediatric neurology evaluation because of hyperactive behavior and failure to achieve the level of academic potential expected in school. Signs of minimal brain dysfunction were recognized on examination and tests of perception revealed deficits in visual and/or auditory channels despite normal intelligence.</td>
<td>6-26 months (mean=16 months)</td>
<td>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</td>
</tr>
</tbody>
</table>
| Safer | 1973 | U.S. (Fair) | Retrospective cohort (student health records) Setting: six elementary schools in Baltimore, Maryland | Hyperactive children who received stimulant medication for >/= 2 years | ≥ 2 years | DEX
MPH
Unmedicated controls
Mean dosages NR |
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Concomitant medication</th>
<th>Safety Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Screened Eligible Enrolled</th>
<th>Withdrawn Lost to fu Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gualtieri</td>
<td>1985</td>
<td>U.S.</td>
<td>Not reported</td>
<td>Monthly clinic visits, NOS.</td>
<td>Mean age 27.2</td>
<td>100% male</td>
<td>Ethnicity NR (represents n=22, of which 8 were included in the long-term followup study)</td>
<td>NR/NR/8</td>
<td>3 withdrew Lost to fu NR 0 analyzed (results described per individual)</td>
</tr>
<tr>
<td>Millichap</td>
<td>1977</td>
<td>U.S.</td>
<td>NR</td>
<td>Measurements of height and weight were made by the author at the times of initial neurologic examination and at re-examination during treatment</td>
<td>Mean age nr 100% male</td>
<td>Race NR</td>
<td></td>
<td>NR/NR/36</td>
<td>NR</td>
</tr>
<tr>
<td>Safer</td>
<td>1973</td>
<td>U.S.</td>
<td>NR</td>
<td>School nurses completed a form based on review of school health records</td>
<td>Mean age nr 89.8% male in children on medication; 100% male in unmedicated control group 100% white</td>
<td>NR/NR/44 on medication, 14 unmedicated controls</td>
<td>NR</td>
<td>44 on medication (DEX=29, MPH=20), 14 unmedicated controls</td>
<td>NR</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Safety Outcomes</td>
<td>Comments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>------</td>
<td>---------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gualtieri</td>
<td>1985</td>
<td>U.S.</td>
<td>One subject consumed a month's supply of MPH in &quot;an abortive suicide attempt&quot;.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Millichap</td>
<td>1977</td>
<td>U.S.</td>
<td>Patients that lost weight: 2/36 (5.5%)</td>
<td>Height: 22 (61.1%) / 23 (64%) Decrease rate of growth: 2 (5.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td>Height: 22 (61.1%) / 23 (64%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All differences remained significant following a covariance analysis that controlled for differences in initial values of weight and height percentiles</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safe</td>
<td>1973</td>
<td>U.S.</td>
<td>DEX: MPH: high-dose (&gt; 20 mg), all, low-dose (≤ 20 mg); controls  DEX &gt; all MPH dosage groups and controls; MPH high-dose and all doses &gt; controls; MPH low-dose=controls</td>
<td>Initial weight/height percentile values were initially larger for DEX group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td>Height: -13.45; -9.40; -5.20; -1.00; +1.29  DEX &gt; MPH all-dosage, low-dosage and control groups, but DEX=MPH high-dosage group; MPH high-dosage &gt; controls; MPH all-dosage and low-dosage=controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Design</td>
<td>Eligibility Criteria</td>
<td>Duration</td>
<td>Interventions (mean dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
<td>---------</td>
<td>------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>---------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeiner</td>
<td>1995</td>
<td>Norway</td>
<td>Prospective cohort study</td>
<td>Boys, between the ages of 7-12 years, DSM-III diagnosis of ADHD</td>
<td>Mean=634 days</td>
<td>Medicated (MPH 23 mg) vs unmedicated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td>Setting: Child psychiatric  outpatient unit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Safer    | 1975 | NR     | Prospective cohort study     | only children who remained in the school for one calendar year were included in the evaluation. Those children whose therapy was changed from one stimulant medication to another during the calendar year, or was discontinued during the school year, were also excluded | I year   | MPH: 27mg/day, range 10-60mg  
dextroamphetamine 12mg/day, range 5-20mg |
## Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Concomitant medication</th>
<th>Safety Assessment</th>
<th>Age</th>
<th>Screened</th>
<th>Eligible</th>
<th>Enrolled</th>
<th>Withdrawn</th>
<th>Lost to fu</th>
<th>Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeiner</td>
<td>1995</td>
<td>Norway</td>
<td>Medicated: no cc meds Unmedicated: 3 (13%) on imipramine x 6 weeks; 1 (4%) on imipramine x 6 months</td>
<td>measurements for height, weight, heartrate and blood pressure.</td>
<td>mean age 9.0 yrs 100% male Ethnicity NR</td>
<td>36/25/23</td>
<td>0/0/23</td>
<td>analyzed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safer</td>
<td>1975</td>
<td>NR</td>
<td>NR</td>
<td>the height and the weight were recorded by two independent examiners</td>
<td>Mean age: 10.3 years, range 8-13 years Gender: 80% male 100% Caucasian</td>
<td>66/NR/NR</td>
<td>NR/NR/26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Safety Outcomes</td>
<td>Comments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
<td>-----------</td>
<td>------------------------------------------------------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeiner</td>
<td>1995</td>
<td>Norway</td>
<td>Measurements at end of treatment: Medicated (n=23) vs unmedicated (n=23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Fair)</td>
<td>Weight: 42.0 vs 40.3; p=NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Height: 150.4 vs 148.3; p=NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safer</td>
<td>1975</td>
<td>(Poor)</td>
<td>Compare growth rate in school year and summer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Continued group (CG): growth rate of the height and weight, NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Discontinued group (DG):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dextroamphetamine, weight- school year&lt;summer, p&lt;0.005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dextroamphetamine, height- school year&lt; summer, p&lt;0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MPH, weight- school year&lt;summer, p&lt;0.005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MPH, height- school year&lt; summer, p&lt;0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Design</td>
<td>Eligibility Criteria</td>
<td>Duration</td>
<td>Interventions (mean dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>--------------------</td>
<td>---------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------</td>
<td>-------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Elementary School Children - Stimulants (combined therapy)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rao</td>
<td>1998</td>
<td>U.S./Canada (Fair)</td>
<td>Cohort, retrospective Setting: National Cooperative Growth Study (NCGS) Database</td>
<td>1) diagnosis of IGHD or ISS (max stimulated GH level &lt; 10 µg/L for IGHD and ≥ 10 µg/L for ISS); 2) no GH therapy before enrollment; 3) prepubertal at enrollment; 4) between 3 and 20 years of age at enrollment; 5) height below the 5th percentile for age and sex; 6) no other significant medical conditions that affect growth; and 7) height reported after at least 180 of GH therapy. Patients who met the criteria and who also were treated for ADHD with MPH or pemoline</td>
<td>NR</td>
<td>MPH or pemoline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean dosages NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weizman</td>
<td>1987</td>
<td>Israel (Fair)</td>
<td>Before-after, prospective Setting: NR</td>
<td><strong>Patients</strong>: ADDH and (1) regular attendance at school, (2) cooperative parents and teacher willing to fill out the Conners rating scale, (3) IQ &gt; 80; (4) absence of significant medical or neurological disease; (5) all patients were drug free for at least 3 months <strong>Controls</strong>: No psychopathology was observed in the subjects or their parents. All subjects were free of lifetime psychiatric disorder</td>
<td>9 weeks</td>
<td>MPH 10.3 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horrigan</td>
<td>2000</td>
<td>U.S. (Fair)</td>
<td>Before-after, retrospective Setting: University-based neuropsychiatric clinic</td>
<td>Adult outpatients with ADHD (DSM-IV 314.01, combined type)</td>
<td>12 months</td>
<td>Adderall (modal dose 10 mg - bid dosing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Concomitant medication</th>
<th>Safety Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Screened</th>
<th>Eligible</th>
<th>Enrolled</th>
<th>Withdrawn</th>
<th>Lost to fu</th>
<th>Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rao</td>
<td>1998</td>
<td>U.S./Canada</td>
<td>NR</td>
<td>Information from case report forms</td>
<td>Mean age=9.3 years</td>
<td>74.8% male</td>
<td>Race NR</td>
<td>NR</td>
<td>NR</td>
<td>3897 enrolled</td>
<td>n/a</td>
<td>n/a</td>
<td>Analyzed: IGHD-ADHD=184; IGHD=2313; ISS-ADHD=117; ISS=1283</td>
</tr>
<tr>
<td>Horrigan</td>
<td>2000</td>
<td>U.S.</td>
<td>SSRI (sertraline or venlafaxine)</td>
<td>Motor tic</td>
<td>Mean age=33</td>
<td>50% male</td>
<td>Ethnicity NR</td>
<td>NR/NR</td>
<td>NR/24</td>
<td>24</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Elementary School Children - Stimulants (combined therapy)**

- **Rao** 1998 U.S./Canada (Fair) NR Information from case report forms
  - Mean age=9.3 years
  - 74.8% male
  - Race NR
  - 3897 enrolled

- **Weizman** 1987 Israel (Fair) NR Blood samples for GH were obtained at 8:00-9:00 am after an overnight fast as follows: (1) morning before treatment initiation; (2) 2 hours after first dose; (3) after 4 weeks; (4) 2 hours after repeated challenge with MPH 5 mg
  - Plasma GH levels were determined by double antibody RIA using materials provided by SORIN S.P.A. (France)
  - Mean age=8.8 years
  - 81% male
  - Race NR
  - 16 patients/16 controls

**Adults**

- **Horrigan** 2000 U.S. (Fair) SSRI (sertraline or venlafaxine) in 4 patients
  - Mean age=33
  - 50% male
  - Ethnicity NR
  - NR/NR/24
  - 24
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Safety Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elementary School Children - Stimulants (combined therapy)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Rao     | 1998 | U.S./Canada (Fair) | Factors w/significant effect on GH-therapy response (stepwise multiple regression):  
MPH/pemoline-treatment: Regression-coefficient= -0.17; contribution to R 2= 0.002; p=0.001 |
| Weizman | 1987 | Israel (Fair)   | GH (ng/ml) in ADDH patients  
Pre-treatment:  
0': 2.6, p=NS  
120': 5.9, p=NS  
Post-treatment:  
0': 2.1; p=NS  
120': 7.8; p=p<0.05  
GH in controls: NR |
| Horrigan| 2000 | U.S. (Fair)    | Motor tic: 1/24 (4%)                                                            |
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>Eligibility Criteria</th>
<th>Duration</th>
<th>Interventions (mean dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghuman</td>
<td>Retrospective cohort (chart review)</td>
<td>(1) a DSM-IV diagnosis of ADHD; (2) psychostimulant treatment initiated between the ages of 3 and 5 years; (3) chart documentation of clinical status both before and during psychostimulant treatment; and (4) follow-up completed for 24 months</td>
<td>24 months</td>
<td>Mean dosages at 3-, 12- and 24-months: MPH: 11.65, 20.8, and 26.67 mg Amphetamine (DEX or Adderall): 7.5, 15.4 and 2.5 mg</td>
</tr>
</tbody>
</table>
## Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Concomitant medication</th>
<th>Safety Assessment</th>
<th>Age</th>
<th>Gender</th>
<th>Ethnicity</th>
<th>Screened</th>
<th>Eligible</th>
<th>Enrolled</th>
<th>Withdrawn</th>
<th>Lost to fu</th>
<th>Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghuman</td>
<td>2001</td>
<td>U.S.</td>
<td>Psychotropic medications (unspecified) for mood disorders, anxiety disorders, and obsessive-compulsive disorder</td>
<td>Clinic notes of Side Effects Rating Form (SERF) ratings</td>
<td>Mean age=4.7 years</td>
<td>85.2% male</td>
<td>52% white</td>
<td>48% black</td>
<td>71/27/27</td>
<td>0 lost to fu</td>
<td>Analyzed: 12 months=23, 24 months=21</td>
<td>6 (22.2%) withdrawn</td>
<td>0 lost to fu</td>
</tr>
</tbody>
</table>
### Evidence Table 15. Observational Studies - Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Safety Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Average weight gain (mean/expected/percentil)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Month 3 (n=25): 0.6 kg/0.6 kg/nr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Month 12 (n=20): 0.6 kg/2.0/75th</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Month 24 (n=14): 2.6 kg/5.0/75th</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Average height gain (mean) (all as expected):</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Month 3 (n=17): 1.8 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Month 12 (n=18): 5.6 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Month 24 (n=12): 11.4 cm</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 16. Quality of Observational Studies of Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Non-biased selection?</th>
<th>Low overall loss to follow-up?</th>
<th>Adverse events pre-specified and defined?</th>
<th>Ascertainment techniques adequately described?</th>
<th>Non-biased and adequate ascertainment methods?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brehaut 2003</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gadow 1999</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ghuman 2001</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
</tr>
<tr>
<td>Gross 1976</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gualtieri 1985</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
</tr>
<tr>
<td>Horrigan 2000</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
</tr>
<tr>
<td>Kratochvil 2001</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Mattes 1983</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>McNutt 1976a (preliminary report)</td>
<td>Unclear; # of children in short-term studies NR</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>McNutt 1976b</td>
<td>Unclear</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Millichap 1977</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Quinn 1975</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
# Evidence Table 16. Quality of Observational Studies of Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Statistical analysis of potential confounders?</th>
<th>Adequate duration of follow-up?</th>
<th>Overall adverse event assessment quality</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brehaut 2003</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Gadow 1999</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Ghuman 2001</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair-Poor</td>
<td></td>
</tr>
<tr>
<td>Gross 1976</td>
<td>NR</td>
<td>Yes</td>
<td>Fair</td>
<td>Study included only patients within the investigator's clinical practice, for whom pre-treatment weight and height data were available.</td>
</tr>
<tr>
<td>Gualtieri 1985</td>
<td>NR</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Horrigan 2000</td>
<td>NR</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Kratochvil 2001</td>
<td>Yes</td>
<td>No</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Mattes 1983</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>McNutt 1976a</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>McNutt 1976b</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Millichap 1977</td>
<td>No</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>Quinn 1975</td>
<td>NR</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence Table 16. Quality of Observational Studies of Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Non-biased selection?</th>
<th>Low overall loss to follow-up?</th>
<th>Adverse events pre-specified and defined?</th>
<th>Ascertainment techniques adequately described?</th>
<th>Non-biased and adequate ascertainment methods?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rao 1998</td>
<td>Yes</td>
<td>n/a</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Safer 1973</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Safer 1975</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
</tr>
<tr>
<td>Safer 1972</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Satterfield 1979</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Weizman 1987</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wernicke 2003</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes for ECG; unclear for adverse events</td>
</tr>
<tr>
<td>Wilens 2003</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zeiner 1995</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
</tr>
</tbody>
</table>
## Evidence Table 16. Quality of Observational Studies of Long-term Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Statistical analysis of potential confounders?</th>
<th>Adequate duration of follow-up?</th>
<th>Overall adverse event assessment quality</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rao</td>
<td>Yes</td>
<td>Unclear</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safer</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>1973</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safer</td>
<td>No</td>
<td>Yes</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>1975</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safer</td>
<td>NR</td>
<td>Yes</td>
<td>Fair</td>
<td>Main outcome (percentile change) uses two timepoints (single baseline measurement taken at school admission at age 5-6, to end of 2+ year treatment) rather than construction of individual growth curves. Classification of treatment during summer based on child's self-report, rather than prescription records.</td>
</tr>
<tr>
<td>1972</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satterfield</td>
<td>NR</td>
<td>Yes</td>
<td>Good</td>
<td>Adherence was assessed by monthly urinalysis.</td>
</tr>
<tr>
<td>1979</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weizman</td>
<td>No</td>
<td>No</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wernicke</td>
<td>Unclear</td>
<td>Yes</td>
<td>Fair</td>
<td>Study selected for MPH responders, decreasing likelihood of AEs.</td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilens</td>
<td>NR</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeiner</td>
<td>Yes</td>
<td>Yes</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>