

# Drug Class Review on Pharmacologic Treatments for ADHD



## Update #3: Preliminary Scan Report

October 2008

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

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## OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

## Date of Last Update:

November 2007 (searches through March 2007)

## Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for ADHD. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. Evidence on Effectiveness and Efficacy
  - a. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders improve *effectiveness* outcomes?
  - b. What is the *comparative* efficacy of different pharmacologic treatments for attention deficit disorders?
2. Tolerability, Serious Adverse Events, Misuse and Diversion
  - a. What is the evidence of *comparative* tolerability of different pharmacologic treatments for attention deficit disorders?
  - b. What is the evidence of serious adverse effects associated with use of pharmacologic treatments for attention deficit disorders?
  - c. What is the comparative or noncomparative evidence that pharmacologic treatments for attention deficit disorders increases the risk of misuse or illicit diversion in patients with no history of misuse or diversion?

- i. stimulants vs. nonstimulants
  - ii. immediate release vs. long-acting formulations
  - iii. Any included pharmacologic treatment
3. Evidence in Subgroups of Patients
- a. What is the evidence of benefits and harms of pharmacologic treatments for attention deficit disorders in subgroups of patients based on demographics (age, racial groups, gender), other medications or therapy, or co-morbidities (e.g. tics, anxiety, substance use disorders, disruptive behavior disorders)?
  - b. What is the comparative or noncomparative evidence of misuse or illicit diversion of pharmacologic treatments for attention deficit disorders in patients with current or past substance use disorder comorbidities?
    - i. stimulants vs. nonstimulants
    - ii. immediate release vs. long-acting formulations
    - iii. Any included pharmacologic treatment

## Inclusion Criteria

### *Populations*

Pediatric, adolescent and adult outpatients with Attention Deficit Disorders

- Attention Deficit Disorder
- Attention Deficit Hyperactivity Disorder

*Interventions (immediate release and extended release formulations, where applicable)*

**Table 1. ADHD drugs and doses**

Generic Name	Trade Name*	FDA ADHD Approval	Year Introduced
MAS**	Adderall <sup>®*†</sup>	Children	1960
	Adderall XR <sup>®***</sup>	Children, adolescents, and adults	2001
Atomoxetine HCl	Strattera <sup>®</sup>	Children and adults	2002
Dextroamphetamine sulfate	Dexedrine <sup>®*</sup>	Children	1976
	Dextrostat <sup>®*†</sup>	Children	1975
Dexmethylphenidate HCl	Focalin <sup>®*†</sup>	Children	2001
	Focalin XR <sup>®†</sup>	Children	2005
Lisdexamfetamine dimesylate	Vyvanse <sup>®</sup>	Children	2007
Methamphetamine hydrochloride	Desoxyn <sup>®†</sup>	Children	1943
Methylphenidate HCl	Biphentin <sup>®†</sup>	N/A	N/A
	Concerta <sup>®</sup> (MPH OROS)	Children and adolescents	2000
	Daytrana <sup>†</sup> (Transdermal patch)	Children	2006
	Metadate CD <sup>®†</sup> (MPH CD)	Children	2001
	Metadate ER <sup>®†</sup> (MPH ER)	Children and adults	1999
	Methylin <sup>®†</sup>	Children and adults	2003
	Ritalin <sup>®*</sup>	Children and adults	1955
	Ritalin SR <sup>®</sup> (MPH SR)	Children and adults	1982

Generic Name	Trade Name*	FDA ADHD Approval	Year Introduced
	Ritalin LA <sup>®†</sup> (MPH SODAS)	Children	2002
Modafinil	Provigil <sup>®</sup>	Adults	1998

\*or generic equivalent

\*\* (amphetamine aspartate; amphetamine sulfate; dextroamphetamine saccharate; dextroamphetamine sulfate)

\*\*\*Notice of Compliance (NOC) suspended in February 2005 by Health Canada in response to case reports of sudden/cardiac death and/or stroke. NOC was reinstated in August 2005 and is again available for prescription in Canada

†Not available in Canada

‡Not available in the United States

### ***Outcomes***

- Symptom response (inattention, hyperactivity-impulsivity, aggression, global ratings, etc.)
- Functional capacity (social, academic, and occupational productivity)
- Caregiver satisfaction (parent, teacher)
- Quality of life (child, parent, caregivers, teachers)
- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (hepatotoxicity, insomnia, anorexia, effects on growth, abuse potential)
- Misuse/diversion (trading, selling, compliance, overdose, development of substance abuse disorders)
- Time to onset of effectiveness
- Duration of effectiveness

### ***Scales and Tests Used to Measure Outcomes***

Numerous ADHD-specific and other psychiatric rating scales, as well as neuropsychological testing methods, are used to measure symptoms of ADHD. We limited our analyses to rating scales/tests for which we found published evidence of good reliability and validity. Our primary sources for documentation of the psychometric properties of rating scales included the Agency for Healthcare Research and Quality (AHRQ), Technical Review #3 (Diagnosis of Attention-Deficit/Hyperactivity Disorder), and Mental Measurements Yearbooks. The AHRQ Technical Review #3 provides qualitative information on many of the rating scales cited in our report, including “subscales included in each test, comorbid conditions addressed by each checklist, time required to administer, number of items, ages for which norms are available, computer scoring availability, and ordering information, including cost” and reliability and validity. Appendix A provides a listing of commonly used scales and tests and associated acronyms.

### ***Study Designs***

- Controlled clinical trials and good-quality systematic reviews
- Observational studies with functional or adverse event outcomes

## **METHODS**

### **Literature Search**

To identify relevant citations, we searched MEDLINE (March 2007 to October 2008). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote X1).

## Study Selection

Two reviewers assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## RESULTS

### Overview

We identified 262 potentially relevant citations. Of those, there are 29 new potentially relevant controlled clinical trials (Appendix A).

### New Drugs

- January 2008 – Vyvanse (Lisdexamfetamine) 3 additional dosage strengths: 20mg, 40mg, 60mg.

### New Indications

- July 2008 – Strattera [Atomoxetine] – Maintenance of ADHD in adults and children with comorbid anxiety disorder without causing worsening of anxiety.
- June 2008 – Concerta [Methyphenidate HCL, extended release] – Treatment of ADHD in adults 18 years and older.
- April 2008 – Vyvanse [Lisdexamfetamine]– Treatment of ADHD in adults

### New Safety Alerts

- October 2008 - Dextroamphetamine Sulfate 5mg Tablets – tablet size issues
- September 2007 - Provigil [Modafinil] Tablets – Additional warnings of serious and life threatening rashes and angioedema. Psychiatric adverse events such as hallucination, anxiety and suicidal ideation may occur in pediatric patients.
- May 2007 – Desoxyn [Methamphetamine] – Additional warnings of serious cardiovascular events, psychiatric adverse events, long term suppression of growth, seizures, and visual disturbances.
- February 2007 - Attention Deficit Hyperactivity Disorder (ADHD) drug products – Patient Medication Guides should include information on cardiovascular risks and psychiatric adverse events in patients with underlying conditions and certain risks factors for predisposition.

The tables below summarize the new studies published since Update 2 of the DERP report on ADHD drugs. New direct comparative evidence in children is available for several comparisons, including 2 trials of Biphentin®, which is currently available in Canada but not the US, and 3 additional studies of atomoxetine (Table 2). In new placebo controlled trials, more evidence on the effects of atomoxetine and MPH IR on sleep is available, a few new placebo-controlled trials with only efficacy evidence, limited new evidence on quality of life or functional outcomes and 7 new studies in patient subgroups (Table 3). There are also 2 new studies with active drug controls (see Appendix).

Table 2: Head to Head Trials Identified in Scan

	Author Year	Drugs	Comments
1	Amiri, 2008	Modafinil and MPH IR	KQ1
2	Findling, 2008	MPH TD and MPH IR	KQ1
3	Newcorn, 2008	Atomoxetine and MPH OROS	KQ1
4	Schachar, 2008	MPH ER (Biphentin®) and MPH IR	KQ1
5	Weiss, 2007	“a novel long-duration multilayer-release (MLR) methylphenidate” (Biphentin®) and MPH IR	KQ1
6	Faraone, 2007	Atomoxetine and mixed amphetamine salts XR	KQ1 – 3 month outcomes
7	Wang, 2007	Atomoxetine and MPH IR	KQ1 and 3 (China, Korea and Mexico)
8	Sonuga-Barke, 2007	Concerta and Metadate CD	KQ3 – sex differences
9	Parasrampur, 2007	MPH IR and MPH OROS	KQ4 – abuse potential

Table 3: Placebo Controlled Trials Identified in Scan

Drug	#	Outcome or population comments	KQ
Preschool aged			
MPH IR	1	additional publication from PATS trial	KQ1
School aged children			
MPH TD	1	Efficacy: multiple wear-times	KQ1
Atomoxetine	7	QOL, sleep (2), ODD, BPD, Tics (2)	KQ 1, 2, 3
DexMPH	1	Efficacy	KQ1
MPH IR	1	Reading disability	KQ3
MPH ER (Medikinet Retard)	1	ODD	KQ3
Adults			
Atomoxetine	3	Functional outcomes, driving, alcohol use disorders	KQ1, 3
MPH IR	1	Sleep	KQ2
MPH MLR (Biphentin®)	1	Efficacy	KQ1
MPH OROS	1	Efficacy	KQ1

## APPENDIX A

### Update 3 Literature Scan Results: Trials

#### Head to Head Trials: 9

Amiri, S., M.-R. Mohammadi, et al. (2008). "Modafinil as a treatment for Attention-Deficit/Hyperactivity Disorder in children and adolescents: a double blind, randomized clinical trial." Progress in Neuro-Psychopharmacology & Biological Psychiatry **32**(1): 145-9.

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most prevalent psychiatric disorder currently afflicting children and is among the most common chronic conditions affecting school-age children. Modafinil is structurally different from the psychostimulants that are typically used to treat ADHD and has been reported to be effective in improving the symptoms of ADHD. The aim of the present study was to further evaluate, under double blind and controlled conditions, the efficacy of modafinil for ADHD in children and adolescents as compared to methylphenidate. Patients included 60 outpatients, children (47 boys and 13 girls) between the ages of 6-15 who clearly met the DSM-IV-TR diagnostic criteria for ADHD. Subjects were recruited from an outpatient child and adolescent clinic for a 6 week double blind, randomized clinical trial. All study subjects were randomly assigned to receive either treatment with modafinil film coated tablet (in doses of 200-300 mg/day) depending on weight (200 mg/day for <30 kg and 300 mg/day for >30 kg) (group 1) or methylphenidate (in doses of 20-30 mg/day) depending on weight (20 mg/day for <30 kg and 30 mg/day for >30 kg) (group 2). The principal measure of outcome was the Teacher and Parent ADHD Rating Scale-IV. Patients were assessed at baseline and at 21 and 42 days after the medication started. No significant differences were observed between the two groups on the Parent and Teacher Rating Scale scores. Side effects of decreased appetite and difficulty falling asleep were observed more in the methylphenidate group. The results of this study indicate that modafinil significantly improved symptoms of ADHD and was well tolerated and it is beneficial in the treatment of children with ADHD.

Faraone, S. V., S. B. Wigal, et al. (2007). "Forecasting three-month outcomes in a laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children With ADHD." Journal of Attention Disorders **11**(1): 74-82.

**OBJECTIVE:** Compare observed and forecasted efficacy of mixed amphetamine salts extended release (MAS-XR; Adderall) with atomoxetine (Strattera) in ADHD children. **METHOD:** The authors analyze data from a randomized, double-blind, multicenter, parallel-group, forced-dose-escalation laboratory school study of children ages 6 to 12 with ADHD combined or hyperactive/impulsive type. Primary efficacy measures are attention and deportment scores on the SKAMP behavioral rating scale, and secondary efficacy measures are academic performance scores from the PERMP test. **RESULTS:** MAS-XR elicits greater improvements than atomoxetine in each domain within 3 weeks of treatment, including attention, number of math problems attempted and correct, and overall clinical functioning. Treatment differences in each outcome measure at subsequent weeks are projected from generalized estimating equations to become greater with the duration of extension of the treatment regimen. **CONCLUSION:** This study suggests that relative advantages of MAS-XR seen in the first 3 weeks are likely to be maintained in subsequent weeks.

Findling, R. L., O. G. Bukstein, et al. (2008). "A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder." Journal of Clinical Psychiatry **69**(1): 149-59.

**OBJECTIVE:** To evaluate the efficacy and safety of methylphenidate transdermal system compared with placebo, using osmotic-release oral system (OROS) methylphenidate as a reference therapy. **METHOD:** We conducted a 7-week, randomized, double-blind, double-dummy, placebo-controlled trial in children diagnosed with attention-deficit/hyperactivity disorder by DSM-IV-TR criteria, within a community setting. The study was conducted from August 2004 to February 2005. Participants were randomly assigned to 1 of 3 treatments: methylphenidate transdermal system patch plus placebo capsule (N = 100), OROS methylphenidate capsule plus placebo patch (N = 94), or placebo capsule plus placebo patch (N = 88). Over 5 weeks, once-daily doses were optimized using 10-, 15-, 20-, and 30-mg methylphenidate transdermal system patches (9-hour wear time) or 18-, 27-, 36-, and 54-mg OROS methylphenidate capsules. Thereafter, optimal treatment doses were maintained for 2 weeks with blinded ratings of attention, behavior, and academic performance occurring at the end of each week. The primary efficacy measure was the clinician-rated ADHD Rating Scale-Version IV (ADHD-RS-IV). Additional measures included teacher, parent, and other clinician rating scales. Safety and tolerability were assessed throughout the study. **RESULTS:** The mean change from baseline in ADHD-RS-IV scores was greater for participants receiving methylphenidate transdermal system and OROS methylphenidate treatments compared with placebo ( $p < .0001$ ). Similar results were observed for parent and teacher rating scales. More participants receiving active treatments compared with placebo were rated as improved by clinicians and parents ( $p < .0001$ ). Adverse events were generally mild or moderate in intensity, and the most common included decreased appetite, nausea, vomiting, and insomnia. **CONCLUSIONS:** The results of this study suggest that the methylphenidate transdermal system is an efficacious treatment option for children with attention-deficit/hyperactivity disorder. **TRIAL REGISTRATION:** [clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00444574.

Newcorn, J. H., C. J. Kratochvil, et al. (2008). "Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response.[see comment]." American Journal of Psychiatry **165**(6): 721-30.

**OBJECTIVE:** Response to atomoxetine, a nonstimulant norepinephrine-specific reuptake inhibitor, was compared with the effect of osmotic-release oral methylphenidate, a long-acting methylphenidate preparation, in patients with attention deficit hyperactivity disorder (ADHD). **METHOD:** In a large placebo-controlled, double-blind study, patients ages 6-16 with ADHD, any subtype, were randomly assigned to receive 0.8-1.8 mg/kg per day of atomoxetine (N=222), 18-54 mg/day of osmotically released methylphenidate (N=220), or placebo (N=74) for 6 weeks. The a priori specified primary analysis compared response (at least 40% decrease in ADHD Rating Scale total score) to osmotically released methylphenidate with response to atomoxetine and placebo. After 6 weeks, patients treated with methylphenidate were switched to atomoxetine under double-blind conditions. **RESULTS:** The response rates for both atomoxetine (45%) and methylphenidate (56%) were markedly superior to that for placebo (24%), but the response to osmotically released methylphenidate was superior to that for atomoxetine. Each medication was well tolerated, with completion rates and discontinuations for

adverse events not significantly different from those for placebo. Of the 70 subjects who did not respond to methylphenidate, 30 (43%) subsequently responded to atomoxetine. Likewise, 29 (42%) of the 69 patients who did not respond to atomoxetine had previously responded to osmotically released methylphenidate. **CONCLUSION:** Response was significantly greater with osmotically released methylphenidate than with atomoxetine. One-third of patients who received methylphenidate followed by atomoxetine responded better to one or the other, suggesting that there may be preferential responders.

Parasrampur, D. A., K. A. Schoedel, et al. (2007). "Do formulation differences alter abuse liability of methylphenidate? A placebo-controlled, randomized, double-blind, crossover study in recreational drug users." Journal of Clinical Psychopharmacology **27**(5): 459-67.

The primary objective of this study was to determine if the abuse liability of methylphenidate is governed by formulation differences that affect rates of drug delivery. In this double-blind, placebo-controlled, randomized, crossover study, subjects with a history of recreational drug use received single oral doses of placebo, 60 mg of immediate-release methylphenidate (IR) and 108 mg of extended-release methylphenidate (osmotic release oral system [OROS]). Over 24 hours after dosing, blood was collected to determine plasma concentrations of methylphenidate, and subjects completed subjective assessments of abuse liability (Addiction Research Center Inventory, Drug Rating Questionnaire-Subject, and Subjective Drug Value). The abuse-related subjective effects of IR and OROS methylphenidate were statistically significantly different from placebo, confirming the overall validity of the study. Although a higher dose of OROS methylphenidate was used compared with IR methylphenidate (108 mg vs 60 mg), subjective effects were consistently lower for OROS compared with IR methylphenidate (statistically significant for 3 of 6 measures of positive effects), particularly at early time points. In general, pharmacokinetic-pharmacodynamic parameters were correlated from a poor to modest degree, with greater correlations observed for IR methylphenidate. In addition, a post hoc "qualification" method was developed, which demonstrated that pharmacological qualification might improve the assessment of subjective effects. Although requiring epidemiological confirmation, the results suggest that OROS methylphenidate, with its characteristic slow ascending plasma concentration profile, may have lower abuse potential. This conclusion is reflected by lower subjective responses during early hours as compared with the IR formulation with its rapid drug delivery and accompanying greater subjective effects.

Schachar, R., A. Ickowicz, et al. (2008). "Cognitive and behavioral effects of multilayer-release methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder." Journal of Child & Adolescent Psychopharmacology **18**(1): 11-24.

**OBJECTIVE:** The aim of this study was to compare the pharmacodynamics of a new multilayer-release (MLR) formulation methylphenidate (MPH; Biphentin) with immediate-release (IR) MPH (Ritalin) in a double-blind, cross-over, placebo-controlled study in patients with attention-deficit/hyperactivity disorder (ADHD). **METHOD:** Patients were randomized to equivalent doses of MPH as MLR (once per day), IR (twice per day) or placebo. Each treatment was taken for 1 week prior to repeated behavioral and cognitive laboratory evaluations on a single day in each phase of the crossover. **RESULTS:** Two girls and 15 boys 6.8-15.3 years old (mean age 11.3 +/- 2.2 years) participated. Both MLR and IR MPH significantly reduced the Stop Signal Reaction

Time ( $p = 0.0001$ ,  $p = 0.0005$ ), the Errors of Omission on the Continuous Performance Task ( $p = 0.0039$ ,  $p = 0.0001$ ), the IOWA-Conners Inattention/Overactivity Index ( $p = 0.0001$ ,  $p = 0.0001$ ), and increased the Clinical Global Impressions (CGI) Efficacy Index ( $p = 0.0001$ ,  $p = 0.0017$ ) and reduced the CGI Global Improvement Index ( $p = 0.0001$ ,  $p = 0.0006$ ) compared to placebo. Mild adverse events were experienced by 4, 6, and 3 patients on placebo, IR, and MLR MPH, respectively. **CONCLUSIONS:** MLR MPH given once daily produces equivalent improvements in behavioral and cognitive measures, and has a duration of effect at least as long as that of IR MPH given twice daily.

Sonuga-Barke, E. J. S., D. Coghill, et al. (2007). "Sex differences in the response of children with ADHD to once-daily formulations of methylphenidate." Journal of the American Academy of Child & Adolescent Psychiatry **46**(6): 701-10.

**OBJECTIVES:** Studies of sex differences in methylphenidate response by children with attention-deficit/hyperactivity disorder have lacked methodological rigor and statistical power. This paper reports an examination of sex differences based on further analysis of data from a comparison of two once-daily methylphenidate formulations (the COMACS study), which addresses these shortcomings. **METHOD:** Children (184: 48 females; mean [SD] age, 9.58 [1.83] years) entered a double-blind, crossover trial of Concerta, MetadateCD/Equasym XL, or placebo. Attention-deficit/hyperactivity disorder symptoms were recorded at seven time points across the school day on the seventh day of treatment, using a laboratory classroom setting. **RESULTS:** More females had comorbid anxiety disorder. Males and females did not differ with regard to other characteristics. Observed sex differences in pharmacodynamic symptom profiles persisted after controlling for placebo and time 0 hours attention-deficit/hyperactivity disorder scores and the presence of an anxiety disorder. Females had a statistically superior response at 1.5 hours post-dosing and an inferior response at the 12-hour time point relative to their male counterparts, no matter which methylphenidate formulation was being assessed. **CONCLUSIONS:** Dose titration of once-daily formulations of methylphenidate should ideally be based on systematic evidence of response at different periods across the day. The responses of female patients may require additional assessments later in the day to determine the optimal dose.

Wang, Y., Y. Zheng, et al. (2007). "Atomoxetine versus methylphenidate in paediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial." Australian & New Zealand Journal of Psychiatry **41**(3): 222-30.

**OBJECTIVE:** To (i) test whether atomoxetine is non-inferior to methylphenidate in treating symptoms of attention deficit hyperactivity disorder (ADHD) in paediatric patients; and (ii) determine the tolerability of the two drugs. **METHOD:** This double-blind study was conducted in 6- to 16-year-old outpatients with ADHD (DSM-IV) in China, Korea and Mexico (January-October 2004). Patients were randomly assigned to once-daily atomoxetine (0.8-1.8 mg kg<sup>-1</sup> day<sup>-1</sup>);  $n = 164$ ) or twice-daily methylphenidate (0.2-0.6 mg kg<sup>-1</sup> day<sup>-1</sup>);  $n = 166$ ) for approximately 8 weeks. Primary efficacy assessment was the comparison of response rates ( $>$  or  $=40\%$  reduction from baseline to end point in total score) on the Attention Deficit Hyperactivity Disorder Rating Scale-IV-Parent Version: Investigator-Administered and -Scored. Tolerability measures included, but were not limited to, the assessment of treatment-emergent adverse

events (TEAEs) and weight. RESULTS: Atomoxetine was non-inferior to methylphenidate in improving ADHD symptoms based on response rates (atomoxetine, 77.4%; methylphenidate, 81.5%; one-sided 95% lower confidence limit = -11.7%,  $p = 0.404$ ). Treatment-emergent adverse effects experienced significantly more frequently in the atomoxetine group, compared with the methylphenidate group, included anorexia (37.2% vs. 25.3%;  $p = 0.024$ ), nausea (20.1% vs. 10.2%;  $p = 0.014$ ), somnolence (26.2% vs. 3.6%;  $p < 0.001$ ), dizziness (15.2% vs. 7.2%;  $p = 0.024$ ) and vomiting (11.6% vs. 3.6%;  $p = 0.007$ ), most of which were of mild or moderate severity. Atomoxetine-treated patients experienced a small but significantly greater mean weight loss from baseline to end point than methylphenidate-treated patients (-1.2 kg vs. -0.4 kg;  $p < 0.001$ ). CONCLUSIONS: This study suggests that atomoxetine is non-inferior to methylphenidate in the improvement of ADHD symptoms in paediatric outpatients. Although both of the drugs were well tolerated, atomoxetine was associated with a higher incidence of TEAEs than methylphenidate.

Weiss, M., L. Hechtman, et al. (2007). "Once-daily multilayer-release methylphenidate in a double-blind, crossover comparison to immediate-release methylphenidate in children with attention-deficit/hyperactivity disorder." Journal of Child & Adolescent Psychopharmacology 17(5): 675-88.

OBJECTIVE: The purpose of this study was to evaluate the comparative efficacy and safety of a novel long-duration multilayer-release (MLR) methylphenidate (MPH) formulation and immediate-release (IR) MPH in attention-deficit/hyperactivity disorder (ADHD) children. PATIENTS AND METHODS: This study was a randomized, double-blind, crossover comparison of once-daily MLR and twice-daily IR-MPH in home and school settings in children with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnosis of ADHD. Patients completed a 1-week baseline followed by two active medication titration phases. Each phase of treatment was 1-4 weeks of titration with an additional stable dose week. The final dose was based on efficacy and adverse events for each patient. Efficacy measures included Clinical Global Impressions (CGI) and Conners' Parent and Teacher Rating Scales (CPRS and CTRS). The Clinical Assessment of Side Effects (CASE) scale assessed frequency of adverse events. RESULTS: Of the 90 enrolled patients, aged 6.4-17.5 years, 79 (88%) completed the study. Stable daily doses were 32.0 and 32.5 mg for MLR and IR-MPH, respectively. All efficacy parameters were significantly improved from baseline. A total of 73.2% and 81.0% of patients on MLR and IR-MPH were rated as "much" or "very much improved" on the CGI. A total of 77.4% and 81.1% of patients were normalized on the CPRS-R and 78.9 and 90.4% of patients were normalized on the CTRS-R for MLR and IR-MPH, respectively. The mean CASE score was not different from baseline for either treatment.

### **Placebo Controlled Trials: 18**

Abikoff, H. B., B. Vitiello, et al. (2007). "Methylphenidate effects on functional outcomes in the Preschoolers with Attention-Deficit/Hyperactivity Disorder Treatment Study (PATs)." Journal of Child & Adolescent Psychopharmacology 17(5): 581-92.

OBJECTIVE: The purpose of this study was to examine the effects of methylphenidate (MPH) on functional outcomes, including children's social skills, classroom behavior,

emotional status, and parenting stress, during the 4-week, double-blind placebo controlled phase of the Preschoolers with Attention Deficit/Hyperactivity Disorder (ADHD) Treatment Study (PATS). METHODS: A total of 114 preschoolers who had improved with acute MPH treatment, were randomized to their best MPH dose (M = 14.22 mg/day; n = 63) or placebo (PL; n = 51). Assessments included the Clinical Global Impression-Severity (CGI-S), parent and teacher versions of the Strengths and Weaknesses of ADHD-Symptoms and Normal Behaviors (SWAN), Social Competence Scale (SCS), Social Skills Rating System (SSRS), and Early Childhood Inventory (ECI), and Parenting Stress Index (PSI). RESULTS: Medication effects varied by informant and outcome measure. Parent measures and teacher SWAN scores did not differentially improve with MPH. Parent-rated depression ( $p < 0.02$ ) and dysthymia ( $p < 0.001$ ) on the ECI worsened with MPH, but scores were not in the clinical range. Significant medication effects were found on clinician CGI-S ( $p < 0.0001$ ) and teacher social competence ratings (SCS,  $p < 0.03$ ). CONCLUSIONS: Preschoolers with ADHD treated with MPH for 4 weeks improve in some aspects of functioning. Additional improvements might require longer treatment, higher doses, and/or intensive behavioral treatment in combination with medication.

Adler, L. A., T. J. Spencer, et al. (2008). "Functional outcomes in the treatment of adults with ADHD." *Journal of Attention Disorders* **11**(6): 720-7.

OBJECTIVE: ADHD is associated with significant functional impairment in adults. The present study examined functional outcomes following 6-month double-blind treatment with either atomoxetine or placebo. METHOD: Patients were 410 adults (58.5% male) with DSM-IV-defined ADHD. They were randomly assigned to receive either atomoxetine 40 mg/day to 80 mg/day (n = 271) or placebo (n = 139). The primary functional outcome measure was the Endicott Work Productivity Scale (EWPS), and the secondary measure was the Adult ADHD Quality of Life (AAQoL). Patients were seen for four visits in 6 months. RESULTS: At 6 months, both groups had nonsignificantly different improvements in EWPS total scores. Atomoxetine-treated patients showed significantly greater improvement than placebo-treated patients on the AAQoL after controlling for baseline severity of ADHD. Both treatment groups had low 6-month study completion rates. CONCLUSION: Following 6-month treatment with atomoxetine, adults with ADHD showed significantly greater improvement in functioning on disease-specific measures of quality of life than patients treated with placebo.

Bangs, M. E., P. Hazell, et al. (2008). "Atomoxetine for the treatment of attention-deficit/hyperactivity disorder and oppositional defiant disorder." *Pediatrics* **121**(2): e314-20.

OBJECTIVE: In this study we examined the effectiveness of atomoxetine for the treatment of oppositional defiant disorder comorbid with attention-deficit/hyperactivity disorder. METHODS: Patients were aged 6 to 12 years and met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, diagnostic criteria for attention-deficit/hyperactivity disorder with a Swanson, Nolan, and Pelham Rating Scale-Revised attention-deficit/hyperactivity disorder subscale score above age and gender norms; Clinical Global Impressions-Severity Scale score of  $>$  or  $= 4$ ; and Swanson, Nolan, and Pelham Rating Scale-Revised oppositional defiant disorder subscale score of  $>$  or  $= 15$ . Patients were randomly assigned in a 2:1 ratio to receive 1.2 mg/kg per day of atomoxetine (n = 156) or placebo (n = 70) for 8 weeks. Treatment effect on oppositional

defiant disorder and attention-deficit/hyperactivity disorder symptoms was measured by using the investigator-rated Swanson, Nolan, and Pelham Rating Scale-Revised. RESULTS: Repeated-measures analysis demonstrated a statistically significant difference favoring atomoxetine over placebo in the reduction of Swanson, Nolan, and Pelham Rating Scale-Revised oppositional defiant disorder total scores. There were significant pairwise treatment differences at weeks 2 and 5 but not at week 8 postbaseline. A last-observation-carried-forward analysis showed Swanson, Nolan, and Pelham Rating Scale-Revised scores at endpoint for the atomoxetine and placebo groups were significantly different for attention-deficit/hyperactivity disorder symptoms but not for oppositional defiant disorder symptoms. Atomoxetine was superior to placebo in a last-observation-carried-forward analysis of Clinical Global Impression-Improvement and Clinical Global Impression-Severity scores. CONCLUSIONS: This study confirms previous findings that patients with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder show statistically and clinically significant improvement in attention-deficit/hyperactivity disorder symptoms and global clinical functioning when treated with atomoxetine. It remains uncertain, however, whether atomoxetine exerts a specific and enduring effect on oppositional defiant disorder symptoms.

Barkley, R. A., D. L. Anderson, et al. (2007). "A pilot study of the effects of atomoxetine on driving performance in adults with ADHD." Journal of Attention Disorders **10**(3): 306-16.

OBJECTIVE: There is a high risk of vehicular crashes, traffic citations, and poorer driving performance in adults with ADHD. This pilot study examines the value of a new nonstimulant (atomoxetine) for improving the driving performance of adults with ADHD. METHOD: Atomoxetine (1.2 mg/kg daily for 3 weeks) and a placebo are studied on 18 adults with ADHD (M age = 37 years) using ratings of ADHD symptoms, impairment, and safe driving behavior; a virtual reality driving simulator; and ratings of simulator performance. RESULTS: Atomoxetine improves self-ratings of ADHD symptoms, impairments, safe driving behavior, and simulator driving performance. No effects of atomoxetine are evident on others' ratings of driving behavior or on the simulator. Practice effects on the simulator may have obscured those drug effects. CONCLUSION: The authors find a mixed pattern of results such that atomoxetine warrants further study for its effects on driving in this high-risk population.

Bental, B. and E. Tirosh (2008). "The effects of methylphenidate on word decoding accuracy in boys with attention-deficit/hyperactivity disorder." Journal of Clinical Psychopharmacology **28**(1): 89-92.

The investigation aimed to delineate the immediate effect of methylphenidate on decoding in the comorbid condition of attention-deficit/hyperactivity disorder and reading disorder. Boys with attention-deficit/hyperactivity and reading disorders (n = 25) between the ages of 7.9 and 11.7 years, with at least average intelligence and verbal processing abilities participated in a double-blind, acute, randomized, placebo-controlled crossover trial with a single dose of methylphenidate 0.3 to 0.4 mg/kg with weekly intervals between testing sessions. The test battery included tasks of attention/control functions and reading domain functions. Paired comparisons and first trial group comparison comparing performance under placebo and under methylphenidate were used. Methylphenidate selectively improved strategy/set shift (P = 0.004) and facilitated improvement both in rapid naming (P = 0.043) and word/nonword accuracy (P = 0.028/P

= 0.035). These findings lend support to a possible influence of methylphenidate on cognitive attention functions related to reading skills in the comorbid group.

Boonstra, A. M., J. J. S. Kooij, et al. (2007). "Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate." *Sleep* **30**(4): 433-42.

**STUDY OBJECTIVES:** To investigate parameters of sleep, activity, and circadian rhythm, as well as the effects of methylphenidate on these variables, in adults with ADHD. **DESIGN:** 1) Baseline group comparison; 2) Double blind, placebo-controlled, cross-over medication trial. **SETTING:** Data collection took place during daily lives of participants. **PARTICIPANTS:** 39 normal controls and 33 adults with ADHD for baseline comparisons; 31 adults with ADHD in medication trial. **INTERVENTIONS:** Treatment with placebo and methylphenidate during medication trial. **MEASUREMENTS AND RESULTS:** Actigraphy and sleep log data were collected for 7 consecutive nights and days to obtain baseline values for ADHD and normal controls. Repeated measurements during placebo and methylphenidate treatment were conducted for the ADHD group. Actigraphic sleep estimates showed that ADHD subjects took longer to fall asleep, had lower sleep efficiency, and had shorter within-night periods of uninterrupted sleep. These findings were consistent with subjective complaints. Actigraphic measures of ADHD subjects showed continuously elevated daytime activity levels, resulting in a 24-hour pattern that was more stable and less variable than in controls. Methylphenidate led to a later bedtime, later sleep onset, and reduction in sleep duration. However, number and total duration of nocturnal awakenings decreased, while mean duration of within-night periods of uninterrupted sleep increased, indicating more consolidated sleep. **CONCLUSIONS:** Our data suggest that sleep problems are inherent in adults with ADHD and that methylphenidate reduced total sleep time but improved sleep quality by consolidating sleep.

Brown, R. T., A. Perwien, et al. (2006). "Atomoxetine in the management of children with ADHD: effects on quality of life and school functioning." *Clinical Pediatrics* **45**(9): 819-27.

The purpose of this study was to examine in a controlled trial the effects of atomoxetine on the management of attention deficit-hyperactivity disorder (ADHD) symptoms and functional impairments at school and at home. Participants were 153 children (age 8 to 12 years) diagnosed with attention-deficit hyperactivity disorder who were randomized to double-blind treatment with either atomoxetine (n = 101) or placebo (n = 52). Findings revealed significant improvements both for parent and teacher ratings of behavior for children receiving atomoxetine therapy. Children also were reported to evidence a trend toward better response to active medication than to placebo for health-related quality of life as rated by parents. No significant effects were revealed for the teacher ratings of academic productivity. Data were interpreted to provide support for the efficacy of atomoxetine on the symptoms associated with ADHD. The effects of atomoxetine on other functional outcomes including academic performance and health-related outcomes are of interest, albeit less compelling for this particular investigation, than for the effects on overt symptom display.

Corkum, P., R. Panton, et al. (2008). "Acute impact of immediate release methylphenidate administered three times a day on sleep in children with attention-deficit/hyperactivity disorder." *Journal of Pediatric Psychology* **33**(4): 368-79.

**OBJECTIVE:** To determine the impact of immediate release Ritalin, given three times a day, on sleep quality and quantity in medication-naive, newly diagnosed children with attention-deficit/hyperactivity disorder (ADHD). **METHODS:** Children (aged 6-12) rigorously diagnosed with ADHD (n = 21) underwent multiple measurement assessments (i.e., actigraphy, sleep diary, and questionnaires) during a 1-week baseline and then during a 3-week blinded randomized medication trial. **RESULTS:** Although the medication was effective in reducing ADHD symptoms, analyses of actigraphy and sleep diary data found statistically and clinically significant changes in the children's total sleep time and sleep onset latency in the medication compared to the no medication conditions. No effects on sleep were found based on the sleep questionnaire. **CONCLUSIONS:** Physicians and parents are encouraged to closely monitor children's sleep when treating ADHD with stimulant medication.

Findling, R. L., E. J. Short, et al. (2007). "Methylphenidate in the treatment of children and adolescents with bipolar disorder and attention-deficit/hyperactivity disorder." Journal of the American Academy of Child & Adolescent Psychiatry **46**(11): 1445-53.

**OBJECTIVE:** To examine the short-term efficacy of methylphenidate in the treatment of youths with bipolar disorder (BD) and comorbid attention deficit/hyperactivity disorder (ADHD). **METHOD:** A 4-week double-blind, placebo-controlled trial in youths ages 5 to 17 years was conducted. Subjects met DSM-IV criteria for bipolar disorder and ADHD, were currently receiving a stable dose of at least one thymoleptic, and while euthymic continued to have clinically significant symptoms of ADHD. Patients received 1 week each of placebo, methylphenidate 5 mg twice daily, methylphenidate 10 mg twice daily, and methylphenidate 15 mg twice daily using a crossover design. Subjects were randomly assigned to receive one of six possible dosing orders. At study's end, and before the blind being broken, a "best dose week" for each subject was determined. The primary outcome measure was the total score on the parent-completed ADHD Rating Scale-IV. **RESULTS:** Sixteen patients, with a mean age of 10.43 (SD 3.14) years completed the trial. Lower scores during best dose treatment compared to the week of placebo treatment were found on the ADHD Rating Scale-IV ( $p < .05$ ), suggesting a therapeutic benefit. A large effect size (Cohen's  $d = 0.90$ ) was found for methylphenidate. Treatment was generally well tolerated. **CONCLUSIONS:** Euthymic youths with bipolar disorder and ADHD may benefit from short-term concomitant treatment with methylphenidate.

Gadow, K. D., J. Sverd, et al. (2007). "Immediate-release methylphenidate for ADHD in children with comorbid chronic multiple tic disorder." Journal of the American Academy of Child & Adolescent Psychiatry **46**(7): 840-8.

**OBJECTIVE:** To examine the safety and efficacy of immediate-release methylphenidate (MPH-IR) for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children (ages 6-12 years) with Tourette's syndrome (96%) or chronic motor tic disorder (4%). **METHOD:** Two cohorts of prepubertal children (N = 71) received placebo and three doses of MPH (0.1, 0.3, and 0.5 mg/kg) twice daily for 2 weeks each, under double-blind conditions as part of their involvement in a long-term observation study (1989-2004). Treatment effects were assessed with an extensive battery of parent-, teacher-, child-, and physician-completed rating scales and laboratory tasks. **RESULTS:** MPH-IR effectively suppressed ADHD, oppositional defiant disorder, and peer aggression

behaviors. There was no evidence that MPH-IR altered the overall severity of tic disorder or obsessive-compulsive disorder behaviors. Teacher ratings indicated that MPH-IR therapy decreased tic frequency and severity. CONCLUSIONS: MPH-IR appears to be a safe and effective short-term treatment for ADHD in the majority of children with chronic tic disorder; nevertheless, the possibility of tic exacerbation in susceptible individuals warrants careful monitoring of all patients.

Gruber, R., N. Grizenko, et al. (2007). "Performance on the continuous performance test in children with ADHD is associated with sleep efficiency." *Sleep* 30(8): 1003-9.

STUDY OBJECTIVE: To examine whether the level of sleep efficiency of children diagnosed with ADHD moderates their performance on the Continuous Performance Test (CPT) while receiving a placebo and while receiving methylphenidate (MPH). DESIGN: Nightly sleep actigraphic assessment during a double-blind, placebo-controlled, crossover clinical study (1 week of 0.5 mg/kg MPH; 1 week of placebo) were obtained on 37 children between 6 and 12 years of age with a DSM-IV diagnosis of ADHD. Subjects were divided into 2 groups based on the mean sleep efficiency score during the placebo condition, with subjects above and below the mean placed in the Poor Sleep Group (PSG) and Good Sleep Group (GSG), respectively. SETTING: Vigilance testing was conducted in the laboratory; sleep was assessed in the home. MEASUREMENTS: Sleep was monitored using actigraphy for 2 weeks. In addition, parents were asked to complete nightly sleep logs and a sleep questionnaire. The Conners' Continuous Performance Test (CPT) was used to assess vigilance. RESULTS: Significant interaction of Sleep Group with Medication was found on 1 CPT factor. CONCLUSIONS: The findings of the present study support the hypothesis that sleep moderates performance on CPT in children with ADHD while receiving placebo or MPH.

Jain, U., L. Hechtman, et al. (2007). "Efficacy of a novel biphasic controlled-release methylphenidate formula in adults with attention-deficit/hyperactivity disorder: results of a double-blind, placebo-controlled crossover study." *Journal of Clinical Psychiatry* 68(2): 268-77.

OBJECTIVE: To evaluate the efficacy and safety of a new biphasic multilayer-release (MLR) methylphenidate formulation in a double-blind, placebo-controlled crossover study of adults with attention-deficit/hyperactivity disorder (ADHD). METHOD: Adults 18 to 60 years of age with a DSM-IV diagnosis of ADHD entered a no-medication baseline week and were then randomly assigned to once-daily MLR methylphenidate or matching placebo. Patients were titrated to optimal effect over 1 to 3 weeks followed by 2 weeks of treatment on a stable dose. The same titration protocol was repeated with the alternate treatment. Clinical Global Impressions scale (CGI) and Conners' Adult ADHD Rating Scales (Self-rated, CAARS-S, and Observer-rated, CAARS-O) were collected at weekly clinic visits. The study was conducted between October 2003 and April 2004. RESULTS: Fifty patients were randomly assigned to treatment, and 39 were analyzed in a per-protocol population (23 men, 16 women; mean age = 37.9 years). CGI-Improvement scores of subjects taking MLR methylphenidate were significantly improved compared with placebo (Global Improvement: 2.6 vs. 3.7;  $p = .0015$ ). MLR methylphenidate produced improvements over placebo on the ADHD Index T scores of the CAARS-S (12.2 vs. 5.4 [change from baseline score];  $p = .0083$ ) and the CAARS-O (10.9 vs. 6.6 [change from baseline score];  $p = .1404$ ). The most frequent adverse events for MLR methylphenidate and placebo were headache (26% and 24%, respectively),

anorexia (22% and 6%), insomnia (22% and 8%), nervousness (20% and 4%), and nausea (16% and 8%). There were no serious adverse events. **CONCLUSIONS:** Once-daily MLR methylphenidate produces significant improvements in ADHD symptoms and situational behavior in adult patients with ADHD, with a prolonged duration of effect and minimal side effects, thus having the potential to improve compliance and, therefore, treatment outcomes in routine clinical use.

Medori, R., J. A. Ramos-Quiroga, et al. (2008). "A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder." Biological Psychiatry **63**(10): 981-9.

**BACKGROUND:** There is increasing recognition of attention-deficit/hyperactivity disorder (ADHD) in adults and the need to evaluate efficacy and safety of methylphenidate treatment in these patients. **METHODS:** In this double-blind trial, 401 adults with ADHD (218 men; 18-63 years) were randomly assigned to receive prolonged-release osmotic release oral system (OROS) methylphenidate (18 mg, 36 mg, or 72 mg/day) or placebo for 5 weeks. Primary outcome was change in total score on Conners' Adult ADHD Rating Scale (CAARS: investigator-rated) at end point compared with baseline. Adverse events, vital signs, and laboratory parameters were assessed.

**RESULTS:** Treatment with 18-mg, 36-mg, and 72-mg/day prolonged-release methylphenidate, compared with placebo, was associated with significantly larger improvement in CAARS total symptom score from baseline to end point than placebo: mean change -10.6 ( $p = .01$ ), -11.5 ( $p = .01$ ), and -13.7 ( $p < .001$ ) versus -7.6, respectively. Responders ( $> \text{ or } = 30\%$  decrease) were 50.5%, 48.5%, and 59.6% versus 27.4% ( $p < .001$ ). Other efficacy measures also showed improvements. Incidence of adverse events was 75%, 76%, and 82% in 18-mg, 36-mg, and 72-mg/day groups, respectively, and 66% in placebo; most frequent included decreased appetite (25% methylphenidate; 7% placebo) and headache (21% methylphenidate; 18% placebo). In methylphenidate-treated patients, 4.3% discontinued due to adverse event; one serious adverse event was possibly related to study drug. Blood pressure and pulse increased at week 1 and then remained stable through week 5. **CONCLUSIONS:** Prolonged-release methylphenidate is an effective treatment of ADHD in adults, with a safety profile consistent with methylphenidate use in pediatrics.

Silva, R. R., R. Muniz, et al. (2008). "Dexamethylphenidate extended-release capsules in children with attention-deficit/hyperactivity disorder." Journal of the American Academy of Child & Adolescent Psychiatry **47**(2): 199-208.

**OBJECTIVE:** This study compared once-daily dexamethylphenidate extended release (D-MPH-ER) 20 mg/day and placebo over 12 hours in children ages 6 to 12 with attention-deficit/hyperactivity disorder (ADHD) in a laboratory classroom setting. **METHOD:** All of the children were stabilized for  $> \text{ or } = 2$  weeks on a total dose (nearest equivalent) MPH 40 mg/day or immediate-release D-MPH 20 mg/day before screening. After a practice day, they received 6 days of D-MPH-ER 20 mg/day or placebo at home, returning on day 7 for one dose. Subjects were evaluated at predose and postdose hours 0.5, 1, 3, 4, 5, 7, 9, 10, 11, and 12 and then crossed over to the other treatment arm using the identical protocol. The primary efficacy variable was the change from predose in Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale (SKAMP) combined score from 1 to 12 hours. Secondary efficacy variables included SKAMP combined score at 0.5

hours, SKAMP subscale scores, and math test results over 12 hours. RESULTS: Sixty-eight children were randomized, with 67 completing the study. Onset of action was indicated by a significant difference between D-MPH-ER and placebo at 0.5 hour on the SKAMP combined score ( $p = .001$ ). For efficacy measures, differences from placebo were significant at all points between 0.5 and 12 hours ( $p < .001$  top = .013). CONCLUSIONS: D-MPH-ER provided sustained improvement in attention, department, and academic productivity throughout the 12-hour laboratory day.

Sinzig, J., M. Dopfner, et al. (2007). "Long-acting methylphenidate has an effect on aggressive behavior in children with attention-deficit/hyperactivity disorder." Journal of Child & Adolescent Psychopharmacology **17**(4): 421-32.

INTRODUCTION: Aggression is frequently observed in children and adolescents with attention-deficit/hyperactivity disorder (ADHD). The aim of this study was to assess the efficacy with regard to oppositional and aggressive behavior of a new long-acting methylphenidate preparation (Medikinet retard, MPH-MR), with equal portions of the immediate-release and the sustained-release active substance, and especially to look at correlations between either teacher or parent assessment of aggression and ADHD sub-symptomatology. METHODS: Eighty five children and adolescents (6-16 years) were investigated in a double-blind, randomized, clinical trial over 5 weeks under a treatment with MPH-MR using symptom checklists for ADHD, oppositional-defiant and conduct disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). RESULTS: A total of 64.9% of the children showed oppositional defiant disorder/conduct disorder (ODD/CD) symptoms. A statistically significant effect was found in the group treated with MPH (verum-group). On the basis of Cohen's criteria, high effects were found for aggressive symptoms in school ( $d = 1.0$ ), but not in the afternoon ( $d = 0.4$ ). There were also lower effect sizes for more severe aggressive symptoms. We found characteristic correlations between ODD/CD symptoms and the ADHD subscale hyperactivity/impulsivity compared to the subscale inattention. CONCLUSIONS: Long-acting MPH is effective in the treatment of oppositional-defiant and aggressive behavior, especially concerning milder symptoms. The expected correlation between impulsivity and aggressiveness could be confirmed.

Spencer, T. J., F. R. Sallee, et al. (2008). "Atomoxetine treatment of ADHD in children with comorbid Tourette syndrome." Journal of Attention Disorders **11**(4): 470-81.

OBJECTIVE: This study examines changes in severity of tics and ADHD during atomoxetine treatment in ADHD patients with Tourette syndrome (TS). METHOD: Subjects (7-17 years old) with ADHD (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV) and TS were randomly assigned to double-blind treatment with placebo ( $n = 56$ ) or atomoxetine (0.5-1.5 mg/kg/day,  $n = 61$ ) for approximately 18 weeks. RESULTS: Atomoxetine subjects showed significantly greater improvement on ADHD symptom measures. Treatment was also associated with significantly greater reduction of tic severity on two of three measures. Significant increases were seen in mean pulse rate and rates of treatment-emergent nausea, decreased appetite, and decreased body weight. No other clinically relevant treatment differences were observed in any other vital sign, adverse event, laboratory parameter, or electrocardiographic measure. CONCLUSION: Atomoxetine is efficacious for treatment of ADHD and its use appears well tolerated in ADHD patients with comorbid TS.

Wilens, T. E., L. A. Adler, et al. (2008). "Atomoxetine treatment of adults with ADHD and comorbid alcohol use disorders." Drug & Alcohol Dependence **96**(1-2): 145-54.

**OBJECTIVE:** Adults with attention-deficit/hyperactivity disorder (ADHD) have higher rates of alcohol and drug use disorders than adults without ADHD. The study aim was to determine if atomoxetine was superior to placebo in improving ADHD and alcohol use in recently abstinent adults with ADHD and comorbid alcohol use disorder. **METHODS:** Adults with DSM-IV diagnoses of ADHD and alcohol abuse and/or dependence were abstinent from alcohol at least 4 days (maximum 30 days) before study randomization. Participants received atomoxetine (25-100mg daily) or placebo for 12 weeks. ADHD symptoms were assessed using ADHD Investigator Symptom Rating Scale (AISRS) total score. Time-to-relapse to heavy alcohol use was analyzed using a 2-sided log-rank test based on Kaplan-Meier estimates and cumulative heavy drinking events over time were evaluated post hoc with recurrent-event analysis. **RESULTS:** Subjects received atomoxetine (n=72) or placebo (n=75) and 80 subjects completed the 12-week double-blind period (n=32 and 48, respectively). ADHD symptoms were significantly improved in the atomoxetine cohort compared to placebo (AISRS total score mean [S.D.], atomoxetine: -13.63 [11.35], P<.001; placebo: -8.31 [11.44], P<.001, difference: P=.007; effect size=0.48). No significant differences between treatment groups occurred in time-to-relapse of heavy drinking (P=.93). However, cumulative heavy drinking days were reduced 26% in atomoxetine-treated subjects versus placebo (event ratio=0.74, P=.023). There were no serious adverse events or specific drug-drug reactions related to current alcohol use. **CONCLUSIONS:** This 3-month, double-blind, placebo-controlled study of atomoxetine in adults with ADHD and comorbid alcohol use disorder demonstrates clinically significant ADHD improvement, and inconsistent effects on drinking behavior.

Wilens, T. E., S. W. Boellner, et al. (2008). "Varying the wear time of the methylphenidate transdermal system in children with attention-deficit/hyperactivity disorder." Journal of the American Academy of Child & Adolescent Psychiatry **47**(6): 700-8.

**OBJECTIVE:** Children with attention-deficit/hyperactivity disorder often have varying needs for coverage of their symptoms throughout the day. The objectives of this study were to determine the efficacy, duration of action, and safety of methylphenidate transdermal system worn for variable times by children (ages 6-12) diagnosed with ADHD. **METHOD:** Methylphenidate dose was optimized over 5 weeks using 10-, 15-, 20-, or 30-mg patches worn for 9 hours. The efficacy of 4- and 6-hour wear times was then assessed in an Analog Classroom setting during a randomized, placebo-controlled, double-blind, three-way crossover phase. The main efficacy measures were the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale department scale and the Permanent Product Measure of Performance math test. **RESULTS:** All of the efficacy measures indicated that 4- and 6-hour wear times improved ADHD symptoms and that medication effects on the Swanson, Kotkin, Agler, M-Flynn, and Pelham Rating Scale department scale and Permanent Product Measure of Performance math test decreased between 2 and 4 hours after patch removal. The majority of adverse events were transient and mild to moderate in severity. **CONCLUSIONS:** These findings suggest that the duration of medication effect is related to the wear time of the patch and may be tailored to accommodate the schedules of patients.

**Active Controlled Trials: 2**

Daviss, W. B., N. C. Patel, et al. (2008). "Clonidine for attention-deficit/hyperactivity disorder: II. ECG changes and adverse events analysis." Journal of the American Academy of Child & Adolescent Psychiatry **47**(2): 189-98.

**OBJECTIVE:** To examine the safety and tolerability of clonidine used alone or with methylphenidate in children with attention-deficit/hyperactivity disorder (ADHD). **METHOD:** In a 16-week multicenter, double-blind trial, 122 children with ADHD were randomly assigned to clonidine (n = 31), methylphenidate (n = 29), clonidine and methylphenidate (n = 32), or placebo (n = 30). Doses were flexibly titrated up to 0.6 mg/day for clonidine and 60 mg/day for methylphenidate (both with divided dosing). Groups were compared regarding adverse events and changes from baseline to week 16 in electrocardiograms and vital signs. **RESULTS:** There were more incidents of bradycardia in subjects treated with clonidine compared with those not treated with clonidine (17.5% versus 3.4%;  $p = .02$ ), but no other significant group differences regarding electrocardiogram and other cardiovascular outcomes. There were no suggestions of interactions between clonidine and methylphenidate regarding cardiovascular outcomes. Moderate or severe adverse events were more common in subjects on clonidine (79.4% versus 49.2%;  $p = .0006$ ) but not associated with higher rates of early study withdrawal. Drowsiness was common on clonidine, but generally resolved by 6 to 8 weeks. **CONCLUSIONS:** Clonidine, used alone or with methylphenidate, appears safe and well tolerated in childhood ADHD. Physicians prescribing clonidine should monitor for bradycardia and advise patients about the high likelihood of initial drowsiness.

Martin, C. A., G. Guenther, et al. (2007). "Measurement of the subjective effects of methylphenidate in 11- to 15-year-old children with attention-deficit/hyperactivity disorder." Journal of Child & Adolescent Psychopharmacology **17**(1): 63-73.

**OBJECTIVE:** This study examined subjective and other behavioral effects of methylphenidate (MPH) among adolescents. **METHODS:** Standard abuse liability assessment methods that have been used in adult populations were modified for attention-deficit/hyperactivity disorder (ADHD) adolescents. MPH effects (0, 0.25 mg/kg) were evaluated under randomized, double-blind conditions in two 5-hour laboratory sessions in 24 (13 female) 11-15 year olds diagnosed with ADHD. **RESULTS:** Repeated measures analysis of covariance indicated significant dose and dose by time interactions on subjective ratings on the modified amphetamine (A) [ $F(1, 20) = 5.98$ ;  $p < 0.05$ ;  $\eta^2 = 0.36$ ], morphine-benzedrine group (MBG) [ $F(1, 21) = 8.93$   $p < 0.01$ ;  $\eta^2 = 0.38$ ] and benzedrine group scale (BG) [ $F(1, 21) = 13.10$   $p < 0.01$ ;  $\eta^2 = 0.37$ ] scales of the Addiction Research Center Inventory; "Hungry" and "How sure are you that you got the medication today?" from the Visual Analogue Scale, the Profile of Mood States Depression scale, performance on the Continuous Performance Task, heart rate and blood pressure, and level of activity. **CONCLUSIONS:** This is the first study to document subjective effects of stimulants in adolescents with ADHD that have been associated with drug abuse potential in adults. There are increasing concerns about nontherapeutic stimulant use in adolescents and young adults. Assessing subjective effects of pharmacotherapies for ADHD along with other measures of abuse potential such as drug self-administration may aid in assessing the therapeutic effects and/or risk of medications

used in the treatment of ADHD.