Pharmacologic Treatment of ADHD Across the Life Cycle: Stimulants

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My spouse/partner and I have the following relevant financial relationships with commercial interests to disclose:


- **Consulting fees:** Akili, Jazz Pharma, and Shire

- **Royalties paid to the Department of Psychiatry at MGH, for a copyrighted ADHD rating scale used for ADHD diagnoses:** Bracket Global, Ingenix, Prophase, Shire, Sunovion, and Theravance

- **Financial interest:** Avekshan LLC, a company that develops treatments for ADHD. My interests were reviewed and are managed by MGH and Partners HealthCare in accordance with their COI policies
Pharmacotherapy of ADHD

- ADHD remains the most treatable disorder in Psychiatry
- Stimulants (amphetamine and methylphenidate compounds) remain the mainstay of treatment for ADHD due to their robust (High Effect Size) efficacy and safety
- FDA-approved Non Stimulants (Atomoxetine and Alpha-2 Agonist (guanfacine and clonidine extended release) are generally less effective than the stimulants (moderate effect sizes of 0.4-0.6)
Effect size is a statistical measure that attempts to represent the magnitude of the treatment effect regardless of sample size.

<table>
<thead>
<tr>
<th>Effect Size</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No effect; each group has the same outcome</td>
</tr>
<tr>
<td>.2</td>
<td>Small effect</td>
</tr>
<tr>
<td>.5</td>
<td>Moderate effect</td>
</tr>
<tr>
<td>.8</td>
<td>Large effect</td>
</tr>
</tbody>
</table>

Effect Sizes of Medications

FDA and Non-FDA approved (all ages)

Effect Size

0.9

0.95

0.62

Stimulants

Long-acting Stimulants

Nonstimulants

No. of studies: 28

Faraone SV. Medscape Psychiatry and Mental Health. 2003;8(2).
Stimulants
Mechanism of Action MPH: Insights from PET Imaging Studies

(Volkow et al. J Att Dis. 2002;(suppl)1)

– Because DA enhances task-specific neuronal signaling and decreases noise, MPH-induced increases in DA could improve attention and decrease distractibility

– Since DA modulates motivation, the increases in DA would also enhance the saliency of the task facilitating the “interest it elicits” and thus improving performance
DVR Images Obtained with $^{[11]}$C]Raclopride After Placebo and After Methylphenidate

Dorsal Anterior Cingulate Cortex (Cognitive Division) Fails to Activate in ADHD

Normal Controls

ADHD

MGH-NMR Center & Harvard- MIT CITP
Bush et al, *Biological Psychiatry* 1999
Methylphenidate Activates Dorsal Anterior Midcingulate Cortex

- fMRI at baseline and again at week 6
- OROS MPH group showed higher daMCC activation at 6 weeks vs placebo
- N=21 adults with ADHD; dosing to 1.3 mg/kg/day OROS MPH or placebo

MTA: Treatment Effects on Inattention Scores (SNAP)

[MTA Group, Arch General Psychiatry, 1999]

![Graph showing treatment effects on inattention scores for parents and teachers. The graph compares different treatment groups (CC, Beh, MedMgt, Comb) across assessment points (days). The y-axis represents average score, ranging from 0 to 3. There are specific points marked on the graph indicating changes in scores over time.]
Teacher SSRS Social Skills

[MTA Group, Arch General Psychiatry, 1999]
Stimulants (FDA approved)
- Methylphenidate
- Amphetamine compounds

(Wilens & Spencer, Postgraduate Medicine, 2010; Adler, Spencer, Wilens 2015)
Types of ADHD Stimulant Formulations

• Immediate-release (IR) Tablets
  – Peak plasma concentrations within 2 hours
• Medium Acting Extended (sustained)-release (XR or SR) (BID)
  – Slow release of drug over 5 to 8 hours
• Medium Acting Spheroidal oral drug absorption system (SODAS) (BID)
  – IR bead and enteric-coated delayed-delivery (DD) bead
• Liquid/Chewable (IR and XR)
• Lisdexamfetamine
• Longer Acting Osmotic release oral system (OROS) (TID)
  – 20% of IR component then 10-12 hour release controlled by osmotic pump
• Longer Acting MAS, triple-bead formulation (Mydayis) (TID)
• Transdermal Formulation (Daytrana)

Duration of Action of ADHD Pharmacotherapy

- Short Acting Tablets: 3-4 hours
- Medium-acting (6-8 hours)
- Long-acting (10-12 hours)
- Longer-acting (16 hours?)

Long Acting MPH formulations
Stimulant Dosing

• Start low and go slow
• Aim: lowest effective dose
• MPH daily dose: 1-1.5 mg/kg/d
• AMPH: 0.5-1.0 mg/Kg/d
• Long acting formulation take on average 1 hr to begin working
• IR formulations: 20-30 min
• Have clear and realistic targets for treatment: ADHD symptoms
Meta-analysis of Within-Subject Comparative Trials Evaluating Response to Stimulant Medications

Spencer et al. Arch of Gen Psych 2001

- Dextroamphetamine: 25%
- Methylphenidate: 23%
- Equal response to either stimulant: 52%

6 studies
N=274
Long-Term Outcomes of Therapies for ADHD in the MTA Study

Hyperactive Impulsive Symptoms (Teacher Reports)

- Medication management: 56%
- Combination therapy (medication + behavior therapy): 60%
- Behavioral treatment: 45%
- Community-based treatment: 36%

Improvement at 14 months (%)
Study of MPH in Adult ADHD

DSM-IV ADHD Symptom Checklist

- **Placebo**
- **MPH**

Week 1 to Week 6

- N = 26
- N = 56

D-MPH (Focalin™)*

An Isomeric Form of MPH

I (-) Methylphenidate

D (+) Methylphenidate

*FDA approved for ADHD.

Courtesy of T. Wilens, MD.
Study of MAS XR in Adult ADHD

Dose Response of Efficacy

CGI-I improvement includes “very much improved” and “much improved”

% Improved

MAS XR 20 mg
MAS XR 40 mg
MAS XR 60 mg

LOCF

P = .0410 for linear dose response trend at Week 4 by MH Chi-square test.

Wilens T. Presented at: 157th Annual APA Meeting; May 1-6, 2004; New York, NY.
Mixed Amphetamine Salts XR Study in Youth with ADHD: CGIS-T Mean Total Score Afternoon

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Add XR 10 mg</th>
<th>Add XR 20 mg</th>
<th>Add XR 30 mg</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10</td>
<td>10.1</td>
<td>10.2</td>
<td>10.3</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Н.Я.</td>
<td>-5.0</td>
<td>-6.0</td>
<td>-7.0</td>
</tr>
<tr>
<td>Change</td>
<td>Н.Я.</td>
<td>-5.0</td>
<td>-6.0</td>
<td>-7.0</td>
</tr>
</tbody>
</table>

ITT Population
- Baseline
- Endpoint
- Change

* P < 0.001 (Dunnett test compared to placebo following ANCOVA with baseline score as covariate)

(Biederman et al., Pediatrics 2003)
Study of MAS in Adult ADHD

DSM-IV ADHD Symptom Checklist

Placebo

Subthreshold ADHD

MAS

Baseline

Week 1

Week 2

Week 3

P<.001

P<.001

Study of MAS XR in Adult ADHD (cont’d)

ADHD-RS: Mean Total Score at Endpoint (ITT)

- Placebo: 26.4
- MAS XR 20 mg: 18.5 *
- MAS XR 40 mg: 18.4 *
- MAS XR 60 mg: 18.5 *

N = 248 adults (≥18 years); 4-week study

* P ≤ .001, adjusted Dunnett test compared with placebo after ANCOVA with baseline score as covariate.

Wilens T. Presented at: 157th Annual APA Meeting; May 1-6, 2004; New York, NY.
LDX Chemistry

LDX

Site of cleavage

l-lysine
d-amphetamine
LDX Extraction, Pharmacokinetic and Abuse Liability Studies: Results

- Amphetamine is very difficult to extract from LDX prodrug
- Intravenous administration does not result in appreciable serum amphetamine levels in rat and human studies
- Intranasal administration does not result in appreciable serum amphetamine levels in rat and human studies
- Apparent “saturation” of LDX in gut limits ultimate serum amphetamine levels (e.g., overdose implications)
- Marginally less likeability in human studies

LDX : Duration of Action
SKAMP Time Course

* $P < .0001$, ** $P < .01$, LDX and Adderall XR vs placebo;
LS = Least Square.
A more negative change in ADHD-RS total score indicates greater improvement.

LS=least squares; SE=standard error of the mean.

*P<.0001 (adjusted Dunnett’ s test compared with placebo following ANCOVA with baseline score as covariate).
In ADHD
Stimulants Found to Improve

Core Symptoms

- Inattention
- Impulsivity
- Hyperactivity

AND

- Noncompliance
- Impulsive aggression
- Social interactions
- Academic efficiency
- Academic accuracy

ADHD Practice Parameters. JAACAP 1997;36:85S.
Pharmacological Dissociation Between The Robust Effects Of Methylphenidate On ADHD Symptoms And Weaker Effects On Working Memory

Figure 1: Cohen's d for Improvement From Baseline to Week 6
Adverse Effects of Stimulants

- Adverse effects (AEs) are similar for all stimulants
  - Decreased appetite
  - Insomnia
  - Headache
  - Stomachache
  - Irritability/rebound phenomena

- Rates of these AEs may be high prior to any medical intervention; thus, baseline levels should always be obtained
Blood Pressure and Heart Rate

Over 10 Years in the MTA

No significant treatment-by-time effect was observed on systolic or diastolic blood pressure.

A significant treatment-by-time effect was observed on heart rate (p=0.02), with significantly higher mean heart rates in the groups receiving medication at 14 months, but not afterward.

(Vitiello et al. JAMA 2012)
ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-aged Adults

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Patrick G. Arbogast, PhD
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Wayne A. Ray, PhD
Joe V. Selby, MD, MPH

Context  More than 1.5 million US adults use stimulants and other medications labeled for treatment of attention-deficit/hyperactivity disorder (ADHD). These agents can increase heart rate and blood pressure, raising concerns about their cardiovascular safety.

Objective  To examine whether current use of medications prescribed primarily to treat ADHD is associated with increased risk of serious cardiovascular events in young and middle-aged adults.

Design, Setting, and Participants  Retrospective, population-based cohort study using electronic health care records from 4 study sites (OptumInsight Epidemiology, Tennessee Medicaid, Kaiser Permanente California, and the HMO Research Network), starting in 1986 at 1 site and ending in 2005 at all sites, with additional covariate assessment using 2007 survey data. Participants were adults aged 25 through 64 years with dispensed prescriptions for methylphenidate, amphetamine, or atomoxetine at baseline. Each medication user (n=150,359) was matched to 2 nonusers on study site, birth year, sex, and calendar year (443,198 total users and nonusers).

Main Outcome Measures  Serious cardiovascular events, including myocardial infarction (MI), sudden cardiac death (SCD), or stroke, with comparison between current or new users and remote users to account for potential healthy-user bias.

Results  During 806,182 person-years of follow-up (median, 1.3 years per person), 1,357 cases of MI, 296 cases of SCD, and 575 cases of stroke occurred. There were 107,322 person-years of current use (median, 0.33 years), with a crude incidence per 1,000 person-years of 1.34 (95% CI, 1.14-1.57) for MI, 0.30 (95% CI, 0.20-0.42) for SCD, and 0.56 (95% CI, 0.43-0.72) for stroke. The multivariable-adjusted rate ratio (RR) of serious cardiovascular events for current use vs nonuse of ADHD medications was 0.83 (95% CI, 0.72-0.96). Among new users of ADHD medications, the adjusted RR was 0.77 (95% CI, 0.63-0.94). The adjusted RR for current use vs remote use was 1.03 (95% CI, 0.86-1.24); for new use vs remote use, the adjusted RR was 1.02 (95% CI, 0.82-1.28); the upper limit of 1.28 corresponds to an additional 0.19 events per 1000 person-years at ages 25-44 years and 0.77 events per 1000 person-years at ages 45-64 years.

Conclusions  Among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events. Apparent protective associations likely represent healthy-user bias.

Screening for Cardiac Risk: AHA Guidelines

• **Medical history**
  - Personal congenital or acquired cardiac disease history
  - Family history of cardiac disease (<50 years of age)
  - Palpitations, chest pain, fainting, seizures, post-exercise symptoms
  - Ask about other medications (including OTC)

• **Routine medical exam**

• **Monitor BP and pulse at baseline and follow-up, especially in adults**

• **ECG is not mandatory; obtain when cardiac problems suspected**

• **Routine check of Holter, ECHO is not necessary**

Growth Over Time in Children Treated With MPH

Onset of Tic Disorders in ADHD Probands Stratified by Stimulant Treatment

(Spencer et al., Arch Gen Psych, 1999)
Protective Effect of Stimulants on Comorbidity

Major Depression

$\chi^2_{(1)} = 19.7, \ p < 0.001$

Multiple Anxiety

$\chi^2_{(1)} = 17.8, \ p < 0.001$

Bipolar Disorder

$\chi^2_{(1)} = 3.5, \ p = 0.063$

Protective Effect of Stimulants on Comorbidity

\[ \chi^2_{(1)} = 1.3, \ p=0.258 \]

\[ \chi^2_{(1)} = 21.4, \ p<0.001 \]

\[ \chi^2_{(1)} = 19.9, \ p<0.001 \]

Biederman et al.  
*Pediatrics* 2009
Protective Effect of Stimulants on Comorbidity

\[ \chi^2_{(1)} = 18.4, \ p < 0.001 \]

Biederman et al. *Pediatrics* 2009
Risk for Substance Use Disorder (SUD) Onset in Adults With Untreated ADHD

Risk for SUD (%) vs Age at onset (years)

- Earlier onset
- Higher risk

$P \leq 0.05$, ADHD vs control at end point

SUD in ADHD Youth Growing Up: Overall Rate of Substance Use Disorder

Biederman, Wilens, Mick et al., Pediatric 1999
Onset of **Nicotine Use** in Children and Adolescents with ADHD

Prospective Study of OROS MPH vs. non-ADHD and ADHD

Omnibus test, chi-squared(1) = 8.44, p = 0.04

p = 0.02

% current smoking according to Fagerstrom Tolerance Questionnaire

Not significant (all p > 0.60)
Stimulant treatment for attention-deficit hyperactivity disorder and risk of developing substance use disorder


Conclusions

Stimulant treatment appears to lower the risk of developing substance use disorders and does not have an impact on the development of nicotine dependence in adolescents with ADHD.

At baseline we assessed ADHD, conduct disorder and oppositional defiant disorder. Substance use disorders, nicotine dependence and stimulant treatment were assessed retrospectively after a mean follow-up of 4.4 years, at a mean age of 16.4 years.

Results

Stimulant treatment of ADHD was linked to a reduced risk for substance use disorders compared with no stimulant treatment, even after controlling for conduct disorder and oppositional defiant disorder (hazard ratio (HR) = 1.91, 95% CI 1.10–3.36), but not to nicotine dependence (HR = 1.12, 95% CI 0.45–2.96). Within the stimulant-treated group, a protective effect of age at first stimulant use on substance use disorder development was found, which diminished with age, and seemed to reverse around the age of 18.

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Medication for Attention Deficit–Hyperactivity Disorder and Criminality

Paul Lichtenstein, Ph.D., Linda Halldner, M.D., Ph.D., Johan Zetterqvist, M.Ed., Arvid Sjolander, Ph.D., Eva Serlachius, M.D., Ph.D., Seena Fazel, M.B., Ch.B., M.D., Niklas Långström, M.D., Ph.D., and Henrik Larsson, M.D., Ph.D.

ABSTRACT

BACKGROUND

CONCLUSIONS

Among patients with ADHD, rates of criminality were lower during periods when they were receiving ADHD medication. These findings raise the possibility that the use of medication reduces the risk of criminality among patients with ADHD. (Funded by the Swedish Research Council and others.)

RESULTS

As compared with nonmedication periods, among patients receiving ADHD medication, there was a significant reduction of 32% in the criminality rate for men (adjusted hazard ratio, 0.68; 95% confidence interval [CI], 0.63 to 0.73) and 41% for women (hazard ratio, 0.59; 95% CI, 0.50 to 0.70). The rate reduction remained between 17% and 46% in sensitivity analyses among men, with factors that included different types of drugs (e.g., stimulant vs. nonstimulant) and outcomes (e.g., type of crime).
Medication for ADHD and Criminality
(Lichtenstein et al. NEJM 2012: 367:2006-2014)

Swedish national registers (N= 25,656 with ADHD-about 50% on medications)
Ca. 40% of convictions related to drug offenses (Tx OR=0.6). No difference in type of ADHD medication (stimulants, nonstimulants) or level of crime.

Women-41% reduction
Men- 32% reduction
Accidents and Near Misses

*Indicates P<0.05 after controlling for gender, age, time of day and the age*ADHD interaction

(Reimer et al., submitted)
www.mghcme.org
During the five surprise events, drivers in the medication group were 67% less likely to have a collision than drivers in the placebo group.

LDX = lisdexamfetamine dimesylate

Biederman et al. 2011 submitted
Association Between Medication Use for Attention-Deficit/Hyperactivity Disorder and Risk of Motor Vehicle Crashes

**DESIGN, SETTING, AND PARTICIPANTS** For this study, a US national cohort of patients with ADHD (n = 2,319,450) was identified from commercial health insurance claims between January 1, 2005, and December 31, 2014, and followed up for emergency department visits for MVCs. The study used within-individual analyses to compare the risk of MVCs during months in which patients received ADHD medication with the risk of MVCs during months in which they did not receive ADHD medication.

**CONCLUSIONS AND RELEVANCE** Among patients with ADHD, rates of MVCs were lower during periods when they received ADHD medication. Considering the high prevalence of ADHD and its association with MVCs, these findings warrant attention to this prevalent and preventable cause of mortality and morbidity.

ADHD (n = 2,319,450) was identified from commercial health insurance claims between January 1, 2005, and December 31, 2014, and followed up for emergency department visits for MVCs. The study used within-individual analyses to compare the risk of MVCs during months in which patients received ADHD medication with the risk of MVCs during months in which they did not receive ADHD medication.

**EXPOSURES** Dispensed prescription of ADHD medications.

**MAIN OUTCOMES AND MEASURES** Emergency department visits for MVCs.
Association Between Medication Use and Performance on Higher Education Entrance Tests in Individuals With Attention-Deficit/Hyperactivity Disorder

**DESIGN, SETTING, AND PARTICIPANTS** This cohort study observed 61,640 individuals with a

**EXPOSURES** Periods with and without ADHD medication use.

**RESULTS** Among 930 individuals (493 males and 437 females; mean [SD] age, 22.2 [3.2] years) who had taken multiple entrance tests (n = 2524) and used ADHD medications intermittently, the test scores were a mean of 4.80 points higher (95% CI, 2.26-7.34; P < .001) during periods they were taking medication vs nonmedicated periods, after

**CONCLUSIONS AND RELEVANCE** Individuals with ADHD had higher scores on the higher education entrance tests during periods they were taking ADHD medication vs nonmedicated periods. These findings suggest that ADHD medications may help ameliorate educationally relevant outcomes in individuals with ADHD.

patients were taking medication for ADHD were compared with scores when they were not taking such medication. Data analysis was performed from November 24, 2015, to November 4, 2016.
The Risk of Treatment-Emergent Mania With Methylphenidate in Bipolar Disorder

Conclusions: No evidence was found for a positive association.

Results: Patients on methylphenidate monotherapy displayed an increased rate of manic episodes within 3 months of medication initiation (hazard ratio = 6.7, 95% CI = 2.0–22.4), with similar results for the subsequent 3 months. By contrast, for patients taking mood stabilizers, the risk of mania was lower after starting methylphenidate (hazard ratio = 0.6, 95% CI = 0.4–0.9). Comparable results were observed when only hospitalizations for mania were counted. New treatment is indicated before initiating monotherapy with psychostimulants.
Psychostimulant Treatment and the Developing Cortex in ADHD

Shaw et al. 2009
Figure 6 | Assessment guides management. The management of attention-deficit/hyperactivity disorder (ADHD) considers psychiatric, psychological and medical co-morbidity. DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; ICD-10, International Statistical Classification of Diseases and Related Health Problems, tenth edition; IQ, intelligence quotient.
Figure 7 | Management decision tree. The choice of medication for treating attention-deficit/hyperactivity disorder (ADHD) considers contraindications, personal preferences, psychiatric co-morbidity and the duration of coverage required. Non-pharmacological treatments target residual disability and are used initially for preschool-aged children or when medication is declined by the patient or parent.
Approach to Comorbidity

• Rule# 1: Treat first the more serious disorder
• It is impossible to address management of ADHD in the face of active psychiatric or medical comorbidity
Approach to Management of Comorbidity with Depression and Anxiety

• Assess whether depression and anxiety are primary or secondary to ADHD or its treatment
Approach to Management of Comorbidity with Mood Disorders

- Assess whether mood disorder is unipolar or bipolar
- Critical distinction guiding treatment
- Antidepressants can exacerbate mania in bipolar depression
QUESTIONS?