Pharmacotherapy of Adult ADHD

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# Disclosures

<table>
<thead>
<tr>
<th>Company</th>
<th>Role/Manner of Support</th>
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<tr>
<td>FDA</td>
<td>Research Support</td>
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<td>Department of Defense</td>
<td>Research Support</td>
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<tr>
<td>Alcobra</td>
<td>Consultant, Advisory Board, research support</td>
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<tr>
<td>Avekshan</td>
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<td>Ironshore</td>
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<td>Shire</td>
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<tr>
<td>Sunovion</td>
<td>Consultant, Research Support</td>
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Dr. Spencer receives research support from Royalties and Licensing fees on copyrighted ADHD scales through MGH Corporate Sponsored Research and Licensing.

Dr. Spencer has a US Patent Application pending (Provisional Number 61/233. 686), through MGH corporate licensing, on a method to prevent stimulant abuse.
DVR Images Obtained with $^{[11]}$C]Raclopride After Placebo and After Methylphenidate

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.
Methylphenidate Increases Dorsal ACC & DLPFC in Patients with ADHD

MPH-OROS Higher than Placebo at 6 Weeks

Bush et al. Archives of General Psychiatry. in press
MTA: Treatment Effects on Inattention Scores (SNAP)

[MTA Group, Arch General Psychiatry, 1999]

MTA Group, Arch General Psychiatry, 1999]
Teacher SSRS Social Skills

![Graph showing the average score over assessment points. The graph has four lines representing CC, Beh, MedMgt, and Comb. The x-axis represents assessment points in days, ranging from 0 to 400. The y-axis represents average scores, ranging from 0.7 to 1.5.](www.mghcme.org)
Pharmacotherapy of Adult ADHD

N=51 Studies
N=5,488 Subjects

N=45 Studies
N=6,439 Subjects

Prince, Wilens 2013
Comparison of MPH Concentration Following IR-MPH and OROS-MPH

Methphenidate Concentration (ng/mL) vs Time (hours)
Clinical Ratings of ADHD Symptoms (ADHD-RS)

<table>
<thead>
<tr>
<th>Week</th>
<th>OROS-MPH mg/day</th>
<th>Placebo mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36.0</td>
<td>36.0</td>
</tr>
<tr>
<td>2</td>
<td>58.7±17.8</td>
<td>66.3±12.8</td>
</tr>
<tr>
<td>3</td>
<td>72.6±26.5</td>
<td>82.2±22.4</td>
</tr>
<tr>
<td>4</td>
<td>77.9±29.6</td>
<td>92.2±23.8</td>
</tr>
<tr>
<td>5</td>
<td>81.3±31.0</td>
<td>94.9±25.5</td>
</tr>
<tr>
<td>6</td>
<td>80.9±31.8</td>
<td>96.8±25.9</td>
</tr>
</tbody>
</table>

*P = 0.04*

Biederman et al Biol psych 2006
BRIEF Impairment Stratified by Executive Function Deficit and Treatment Status at Baseline and Endpoint

Biederman et al. Eur Neuropsychopharmacol 2011
Focalin™ (D-MPH)*
An Isomeric Form of MPH

I (-) Methylphenidate

D (+) Methylphenidate

*FDA approved for ADHD.

Courtesy of T. Wilens, MD.
SODAS d-MPH: DAT Occupancy (PET) by Hour and Dose

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
Mixed Amphetamine Salts: Mean Total Score at Endpoint (ITT)

endpoint = LOCF

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Endpoint</th>
<th>Change (Endpoint - Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>33.0</td>
<td>26.4</td>
<td>-6.6</td>
</tr>
<tr>
<td>Adderall XR™ 20mg</td>
<td>31.1</td>
<td>18.5 **</td>
<td>-12.6</td>
</tr>
<tr>
<td>Adderall XR™ 40mg</td>
<td>31.3</td>
<td>18.4 **</td>
<td>-12.9</td>
</tr>
<tr>
<td>Adderall XR™ 60mg</td>
<td>32.9</td>
<td>18.5 **</td>
<td>-14.4</td>
</tr>
</tbody>
</table>

**P ≤ 0.001 (adjusted Dunnett’s test compared with placebo following ANCOVA with baseline score as covariate)
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).
Stimulant Tx of Executive Function
Lisdexamfetamine in Adult ADHD + GEC > 65

Adler et al. JCP 2013
Controlled Trial of Lisdexamfetamine Collisions
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
Concerns Associated with Use of Stimulants

- Substance abuse
- Diversion
- Tics
- Growth
- Cardiovascular risk
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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Marsha A. Raebel, PharmD
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Steve Sidney, MD, MPH
Mai N. Nguyen-Huynh, MD, MAS
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 site 1 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 1,000 person-years at ages 25-44 years and 0.77 events per 1,000 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 reasonable but not mandatory
• Routine check of Holter, ECHO is not necessary

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.
Norepinephrine Effects

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**Attentional Systems**

**Posterior**
- Disengage from stimuli
- Change focus to new stimuli
- Engage attention to new stimuli

**Anterior**
- Working memory
- Analyze data
- Prepare for response

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fMRI of Atomoxetine: MSIT shows activation of
dorsolateral prefrontal, parietal, cerebellum

Atomoxetine: Long-term Efficacy in Adults (34 Weeks)

Mean CAARS Change

- Placebo
- Atomoxetine
- Atomoxetine-EXT

Weeks

Acute Phase
Discontinuation Phase
Extension Phase

Atomoxetine Treatment in Adults with ADHD and Comorbid Social Anxiety Disorder

Adler et al. Depression Anxiety 2009

![Graph showing improvement over weeks for Placebo and Atomoxetine treatments.](image)
# Atomoxetine in Adults with ADHD:
Common Side Effects*

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Atomoxetine (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Insomnia</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Erectile difficulty</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Increased BP (systolic, diastolic): 1-3 mm Hg</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Increased HR: 5 bpm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All significant versus placebo.

Atomoxetine: Black Box Warnings

• **Hepatotoxicity**
  - Two cases in 4 million exposures of elevated liver enzymes (one had autoimmune disease); no clinical predictors
  - Symptoms: Abdominal pain and jaundice
  - Resolved with discontinuation of medication
  - No screening or blood tests necessary

• **Suicidal ideation/behavior is a concern in children only and is extremely rare**

Medications that are not FDA approved for ADHD
Bupropion XL (Wellbutrin XL®) in Adults With ADHD: Percent Responders

- *P ≤ .01, †P < .05, § ≥ 30% reduction from baseline.

Wilens et al. Biol Psych 2005
Armodafinil Intrasympatic Dopamine (Rt Caudate) by Dose

Volkow et al. JAMA 2009

Spencer et al. Biol Psych 2010
Memantine: Clinical ADHD Rating (AISRS)

Surman et al. Annual Meeting AACAP 2010

p < 0.05 vs. baseline

Week (LOCF)
Summary: Pharmacotherapy of ADHD

- Efficacy in adults consistent with efficacy in children
- A variety of effective drugs
- Commonality: dopaminergic or noradrenergic mechanism of action
- Preliminary evidence of cholinergic mechanism