Pharmacotherapy of ADHD Across the Lifecycle: Stimulants

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DVR Images Obtained with $[^{11}\text{C}]$Raclopride After Placebo and After Methylphenidate

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
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]

**Parent**

**Teacher**

- **CC**
- **Beh**
- **MedMgt**
- **Comb**

*Average Score vs. Assessment Point (Days)*
Teacher SSRS Social Skills

![Graph showing average scores over assessment points (days)]
# Methylphenidate (MPH) in ADHD: Optimizing Dosing

*May exceed FDA approved dose.


<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Maximum Dose* Usual Dosing</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin IR®</td>
<td>5 mg QD/BID</td>
<td>2 mg/kg/day</td>
<td>4 hr / BID</td>
</tr>
<tr>
<td>Focalin®</td>
<td>2.5 mg QD/BID</td>
<td>1 mg/kg/day</td>
<td>4–5 hr / BID–TID</td>
</tr>
<tr>
<td>Focalin XR®</td>
<td>5 mg QD</td>
<td>1 mg/kg/day</td>
<td>10–12 hr QD</td>
</tr>
<tr>
<td>Daytrana®</td>
<td>10 mg</td>
<td></td>
<td>6–16 hr</td>
</tr>
<tr>
<td>Concerta®</td>
<td>18 mg QD</td>
<td>2 mg/kg/day</td>
<td>12 hr / once</td>
</tr>
<tr>
<td>Metadate CD®</td>
<td>20 mg QD</td>
<td></td>
<td>8 hr / once</td>
</tr>
<tr>
<td>Ritalin LA®</td>
<td>20 mg QD</td>
<td></td>
<td>8 hr / once</td>
</tr>
<tr>
<td>Quillivant®</td>
<td>&lt;10 mg QD</td>
<td></td>
<td>12 hr / once</td>
</tr>
<tr>
<td>Quillichew™</td>
<td>&lt;10 mg QD</td>
<td></td>
<td>8 hr / once</td>
</tr>
<tr>
<td>Aptensio XR</td>
<td>10 mg QD</td>
<td></td>
<td>12 hr / once</td>
</tr>
</tbody>
</table>
Long Acting MPH formulations

**Concerta**

**Metadate**

**Ritalin**

**Quillivant**

**Focalin**

**Aptensio**
MPH ER Individual PK Plots
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>

Biederman et al. Biol psych 2006
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
Focalin™ (D-MPH)*
An Isomeric Form of MPH

I (-) Methylphenidate

D (+) Methylphenidate

*FDA approved for ADHD.

Courtesy of T. Wilens, MD.
# Amphetamine (AMPH) in ADHD: Optimizing Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting Dose</th>
<th>Maximum Dose*</th>
<th>Usual Dosing</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adderall®</td>
<td>2.5–5 mg QD</td>
<td>1.5 mg/kg/day</td>
<td>6 hr / BID</td>
<td></td>
</tr>
<tr>
<td>Adderall XR®</td>
<td>2.5–5 mg QD</td>
<td></td>
<td>12 hr / QD</td>
<td></td>
</tr>
<tr>
<td>Vyvanse®</td>
<td>30 mg QD</td>
<td></td>
<td>12–14 hr / QD</td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine Tablets®</td>
<td>2.5–5 mg BID</td>
<td>1.5 mg/kg/day</td>
<td>3–5 hr / BID–QID</td>
<td></td>
</tr>
<tr>
<td>Evekeo®</td>
<td>2.5–5 mg BID</td>
<td></td>
<td>3–5 hr / BID–QID</td>
<td></td>
</tr>
<tr>
<td>Dexamphetamine Spansule®</td>
<td>5 mg QD</td>
<td></td>
<td>6 hr / QD–BID</td>
<td></td>
</tr>
<tr>
<td>Dyanavel XR™ (suspension)</td>
<td>2.5–5 mg QD</td>
<td>1.5 mg/kg/day</td>
<td>12 hr / QD</td>
<td></td>
</tr>
<tr>
<td>Adzenys XR™ (disintegrating tab)</td>
<td>6.3–12.5 mg QD</td>
<td>Not established</td>
<td>12 hr / QD</td>
<td></td>
</tr>
</tbody>
</table>

*May exceed FDA approved dose (eg, > 20 to 30 mg/day).

Meta-analysis of Within-Subject Comparative Trials Evaluating Response to Stimulant Medications

6 studies
N=274

Best Response (Percent)

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

Spencer et al. Arch of Gen Psych 2001
18-Month Summary of Symptom Improvement With MAS XR 20, 40, and 60 mg/day

Results of Short-term and 18 Months of Long-term Open-Label Extension Study

Mean ADHD-RS Total Score

*P<.05 by 1-sample t test of mean change from baseline of long-term study.

Wilens T. Presented at: 157th Annual APA Meeting; May 1-6, 2004; New York, NY.
SHP465 Mixed Amphetamine Salts

Wigal et al. 2018

![Graph showing the comparison between Placebo (n=75) and SHP465 MAS (n=73) with mean ± SD PERMP Problems Attempted over time from 2 to 16 weeks.](graph.png)
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

Score

Baseline 2nd Simulation

TX Group Placebo

www.mghcme.org
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
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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Denise M. Boudreau, PhD, RPh
Susan E. Andrade, ScD
Pamela A. Pawlowski, PharmD
Marsha A. Rabell, PharmD
David H. Smith, RPh, PhD
Ninam Achacoso, MS
Connie Urasu, RN
Alan S. Go, MD
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 one 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 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

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.
FDA PK/PD Classroom Study

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