Studying Cardiovascular Risk with Drug Treatments of ADHD

Feasibility of Available Study Methods in Children and Adults

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Division of Drug Risk Evaluation
Studying Cardiovascular Risk of ADHD Drugs – points for discussion today:

- Rationale for safety concern
- Overview of MedWatch reports:
  - Sudden death in children or adults
    - Calculated reporting rates
    - Background incidence
  - Nonfatal cardiovascular or cerebrovascular adverse events
- Challenges? Study options?
- What next?
Rationale for Safety Concern

**Biological plausibility**

- Adrenergic agonists
- Known effects of sympathomimetic drugs on blood pressure, described in some labeling
- Precautions against use in patients with known risk factors such as coronary artery disease, structural cardiac abnormalities
- Some structurally similar compounds have shown safety issues related to their pharmacologic effects in some patients
Rationale for Safety Concern

- Drug treatment of ADHD is increasing in all age groups.
- Drug treatment for ADHD can now potentially be life-long.
Rationale for Safety Concern

Effects on blood pressure and heart rate - adults

- Adults (n=26) treated with amphetamine for ADHD showed statistically significant increase in mean change from baseline for systolic BP and heart rate compared with placebo.
  - Amphetamine: mean change +5.3 mmHg systolic BP, +7.3 heart rate

- Small but statistically significant increases in blood pressure and heart rate seen in adults (n=141) treated with methylphenidate for ADHD in a 6-week randomized placebo-controlled trial.

- Atomoxetine USPI includes Precaution about blood pressure and heart rate increases compared with placebo in clinical trials.
  - Mean increase in systolic (about 3 mmHg) and diastolic (about 1 mmHg) BP
Rationale for Safety Concern

- In adults, usual blood pressure is strongly and directly related to vascular and overall mortality.

Rationale for Safety Concern

**Long-term study of cardiovascular effects in adults:**

- N = 223 otherwise healthy adults (18+ years) with ADHD
- Treated up to 24 months with 20-60 mg/day amphetamine mixed salts
- Statistically significant increases in mean BP and heart rate
- Statistically significant increase in QTc was seen at 24 months
- Seven subjects discontinued study due to cardiovascular adverse event (5 hypertension, 2 tachycardia)

Rationale for Safety Concern

Effects on blood pressure and heart rate - children

- 24-h ambulatory blood pressure monitoring (ABPM)
- Thirteen subjects underwent APBM both on stimulant therapy and placebo using a placebo-controlled, double-blind, randomized, cross-over design (Samuels 2006).
- Total diastolic blood pressure (69.7 mmHg vs 65.8 mmHg, p =0.02) was significantly higher during active treatment.
- Total heart rate was also significantly higher during active treatment (85.5 beats/min vs 79.9 beats/min, p =0.004).


Rationale for Safety Concern

- **Very few long-term studies have been done in children:**

- **These studies have yielded little information on cardiovascular risk.**
Rationale for Safety Concern

- MedWatch cases suggest potential cardiovascular signal in FDA safety reviews, but not conclusive.

- Nonfatal cardiovascular reports include:
  - Syncope
  - Chest pain, MI
  - Stroke
  - Arrhythmias
  - Cases often not well documented

- Sudden death reports:
  - Calculated reporting rates do not exceed background rates, but extent of under-reporting is unknown.
The Committee agreed with the FDA that it is not yet possible to determine whether cardiovascular adverse events, especially the more serious ones, are causally associated with ADHD treatments.

The committee also agreed that the FDA should pursue additional means to better characterize the cardiovascular risks for all drug products approved for ADHD.

Potential options under consideration include population-based pharmacoepidemiologic studies, long term safety trials, and other targeted CV risk studies.
Limitations of Calculating Reporting Rates from Spontaneous Reports

- **Under-reporting**
  - How much?
  - Numerator not reliable for many reasons

- **Lack of good denominator**
  - Poor precision

- **Cannot calculate incidence**
  - Comparison of reporting rates to background incidence or between drugs is only a rough estimate

- **Confounding**
  - Other drugs?
  - Pre-existing conditions?
Review of MedWatch Reports

- Searches conducted of the Adverse Event Reporting System (AERS) safety database.

- Definition of sudden death used in review:
  - Death occurred immediately or within 24 hours of an acute collapse.

- Analysis excluded cases in which:
  1. Death was caused by multi-drug overdose
  2. Drug abuse was reported
  3. Death was most likely due to another cause.
Background Incidence
Pediatric Sudden Unexplained Death

- From NEJM Review article (Liberthson 1996)
  - Lower bound
    - 1.3 cases / 100,000 person-years (p-y)
    - Driscoll 1985 death certificate review, Olmstead County, MN, 1950 – 1982
    - Ages 1 to 22 years at time of death
  - Upper bound
    - 2.4 – 8.5 cases / 100,000 p-y
    - Kennedy et al, St. Louis County, 1981-1982
    - Ages 1 to 29 years

Pediatric Sudden Death (≤ 18 years of age)

<table>
<thead>
<tr>
<th>Drug</th>
<th>All Age Groups</th>
<th>Pediatric Age Group 0 – 18 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Prescriptions¹</td>
<td>Pediatric Exposure (p-y)²</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>110,734,000</td>
<td>7,127,432</td>
</tr>
<tr>
<td>Amphetamine &amp; Dextroamphetamine</td>
<td>70,699,000</td>
<td>3,817,929</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>9,419,000</td>
<td>601,246</td>
</tr>
</tbody>
</table>


² Total person-years (p-y) times the percentage of drug appearances in the pediatric subgroup population (IMS Health, National Disease and Therapeutic Index™, January 1993 to December 2004, Data Extracted June 2005).

³ N = sudden death cases identified in FDA AERS database received from January 1992 through February 2005.

*Note: drugs include both branded and generic, all formulations available during respective time periods.*
Pediatric sudden death case report

ISR number 3782505-X/US

- A pediatrician reported that a 13 year old male collapsed while working at his computer and died suddenly after taking a single dose of amphetamine mixed salts, 20 mg, for the treatment of ADHD.
- He had been seen by a physician for a physical exam the previous day, with complaints of school problems and was diagnosed with ADHD.
- Blood pressure and heart rate were normal. Weight was 118 pounds. He was active in sports.
- The patient took a single 20 mg dose of amphetamine mixed salts, immediate release formulation, at 10:30 am, complained of tiredness about midday, and collapsed at his computer in late afternoon. A pulse was present when emergency personnel arrived, but he was pulseless at the hospital.
- An autopsy showed idiopathic hypertrophic subaortic stenosis (IHSS), and an enlarged heart “filling complete chest”. The number of Adderall tablets was correct in the remaining drug supply. No concomitant medications were reported.
- The reporting physician considered that the cause of death was cardiomegaly and arrhythmia.
## Background Incidence

### Adult Sudden Cardiac Death (age ≥ 35 years)

#### Age-specific death rates: United States, 1998

<table>
<thead>
<tr>
<th>Age-specific rate</th>
<th>N</th>
<th>Men Per 100,000</th>
<th>N</th>
<th>Women Per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-44 y</td>
<td>7533</td>
<td>34.1</td>
<td>2584</td>
<td>11.5</td>
</tr>
<tr>
<td>45-54 y</td>
<td>19,575</td>
<td>115.9</td>
<td>5931</td>
<td>33.5</td>
</tr>
<tr>
<td>55-64 y</td>
<td>30,680</td>
<td>284.0</td>
<td>12,006</td>
<td>101.2</td>
</tr>
<tr>
<td>65-74 y</td>
<td>49,508</td>
<td>600.2</td>
<td>28,874</td>
<td>284.7</td>
</tr>
<tr>
<td>75-84 y</td>
<td>64,863</td>
<td>1362.8</td>
<td>66,727</td>
<td>928.5</td>
</tr>
<tr>
<td>&gt;84 y</td>
<td>48,332</td>
<td>4073.3</td>
<td>119,416</td>
<td>4171.8</td>
</tr>
</tbody>
</table>

### Adult Sudden Death (18+ Years)

<table>
<thead>
<tr>
<th>Drug</th>
<th>All Age Groups</th>
<th>Adult Age Group 0 – 18 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Prescriptions(^1)</td>
<td>Adult Exposure (p-y)(^2)</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>110,734,000</td>
<td>1,764,591</td>
</tr>
<tr>
<td>Amphetamine &amp; Dextroamphetamine</td>
<td>70,699,000</td>
<td>1,857,056</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>9,419,000</td>
<td>142,855</td>
</tr>
</tbody>
</table>


2 Total person-years (p-y) times the percentage of drug appearances in the adult subgroup population (IMS Health, National Disease and Therapeutic Index™, January 1993 to December 2004, Data Extracted June 2005).

3 N = sudden death cases identified in FDA AERS database received from January 1992 through February 2005.

*Note: drugs include both branded and generic, all formulations available during respective time periods.*
Nonfatal Cardiovascular Adverse Effects

Nonfatal cardiovascular adverse events

- Identified as a potential signal in recent FDA reviews based on MedWatch reports
- May be more readily studied in claims databases since they can be identified by ICD-9 codes
- Sudden deaths may be problematic to identify in claims data
## Nonfatal Cardiovascular/Cerebrovascular Serious Adverse Events - Methylphenidate

**Pediatric Age Group, for five year period 1999 - 2003, N = 8 reports**

<table>
<thead>
<tr>
<th>Age</th>
<th>7-18 years (mean 11.5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>5 male, 3 female</td>
</tr>
<tr>
<td>Suspect drug</td>
<td>methylphenidate</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
</tr>
<tr>
<td>syncope</td>
<td>(1)</td>
</tr>
<tr>
<td>loss of consciousness</td>
<td>(1)</td>
</tr>
<tr>
<td>dyspnea</td>
<td>(1)</td>
</tr>
<tr>
<td>palpitations / arrhythmia</td>
<td>(6)</td>
</tr>
<tr>
<td>abnormal heart biopsy</td>
<td>(1)</td>
</tr>
<tr>
<td>cardiac arrest</td>
<td>(1)</td>
</tr>
<tr>
<td>stroke</td>
<td>(1)</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>(1)</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
</tr>
<tr>
<td>none mentioned</td>
<td>(2)</td>
</tr>
<tr>
<td>1 med</td>
<td>(3)</td>
</tr>
<tr>
<td>2 meds</td>
<td>(3)</td>
</tr>
<tr>
<td>Year reported</td>
<td>1999 (0), 2000 (0), 2001 (3), 2002 (1), 2003 (4)</td>
</tr>
</tbody>
</table>
### Nonfatal Cardiovascular/Cerebrovascular Serious Adverse Events - Methylphenidate

**Adult Age Group, for five year period 1999 - 2003, N = 11 reports**

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>33-75 years (mean 50.6 years)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>6 male, 4 female, 1 not reported</td>
</tr>
<tr>
<td><strong>Suspect drug</strong></td>
<td>methylphenidate</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>syncope (2), increased blood pressure / hypertension (3), chest pain (3), heart failure (1), myocardial infarction (3), arrhythmia (2), mitral valve prolapse (1), stroke (1)</td>
</tr>
<tr>
<td><strong>Concomitant medications</strong></td>
<td>none mentioned (6), 1 med (2), 2 meds (2), 3 meds (1)</td>
</tr>
<tr>
<td><strong>Year reported</strong></td>
<td>1999 (3), 2000 (1), 2001 (2), 2002 (3), 2003 (2)</td>
</tr>
</tbody>
</table>
Nonfatal Cardiovascular/Cerebrovascular Serious Adverse Events - Amphetamine

*Pediatric Age Group, for five year period 1999 - 2003, N = 18 reports*

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>7-17 years (mean 11.4 years)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>15 male, 3 female</td>
</tr>
<tr>
<td><strong>Suspect drug</strong></td>
<td>Amphetamine, mixed salts (18)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>syncope (2), increased blood pressure / hypertension (6), dyspnea (4), myocardial infarction (1), arrhythmia (5), left ventricular hypertrophy (1), thromboembolic stroke (1), sub-arachnoid hemorrhage (1)</td>
</tr>
<tr>
<td><strong>Concomitant medications</strong></td>
<td>none mentioned (6), 1 med (7), 2 meds (1), 3 meds (2), 4 meds (2)</td>
</tr>
</tbody>
</table>
Nonfatal Cardiovascular/Cerebrovascular Serious Adverse Events - Amphetamine

**Adult Age Group, for five year period 1999 - 2003, N = 17 reports**

| Age | 19-58 years (mean 42 years) |
| Gender | 11 male, 6 female |
| Suspect drug | amphetamine |
| Serious adverse events | syncope (2), increased blood pressure / hypertension (3), chest pain (4), dyspnea (3), myocardial infarction (5), arrhythmia (6), cardiomyopathy (3), stroke (3), cardiac arrest (2) |
| Concomitant medications | none mentioned (8), 1 med (7), 3 meds (1), 4 meds (1) |
| Year reported | 1999 (2), 2000 (2), 2001 (6), 2002 (0), 2003 (7) |
Nonfatal Cardiovascular/Cerebrovascular Serious Adverse Events - Atomoxetine

- Similar reports for atomoxetine have also been received since FDA approval in November 2002.

- MedWatch reports for atomoxetine include cases of arrhythmia, syncope, cardiac arrest, myocardial infarction, and stroke.

- Reports include both pediatric and adult patients (age range 2 – 70 years).

- Cases currently under review.
Many Challenges

- Acute vs. chronic effects of drugs
- Very different background cardiovascular risk for different age groups
- Unknown impact of confounders such as underlying diseases or abnormalities
- Clinical development programs for newer vs. older ADHD drugs reflect requirements at the time of initial approval.
Study Options for Risk Characterization

- Large simple trial (LST) to assess long term safety outcomes?
  - Power and feasibility – barriers for useful study?
  - Ethical issues include patient / parent acceptability of randomization
  - Who would pay for this?
Possible Current Study Options for Risk Characterization

- Pharmacoepidemiologic approaches:
  - NIMH case-control study of pediatric sudden death
    - Columbia University (Dr Gould)
  - Large, population based epidemiologic study of adverse cardiovascular outcomes
    - FDA Epidemiology Contracts
NIMH-funded Case Control Study

- Principal Investigator:
  - Dr. Madelyn Gould, Ph.D., M.P.H., New York State Psychiatric Institute

- Major aim of study: to examine the relationship between sudden death in children and adolescents and the use of
  - tricyclic antidepressants, or
  - concomitant methylphenidate and clonidine therapy

- Cases: pediatric sudden deaths during the period 1985 - 1996, identified using state vital statistics data

- Target number of cases: 400 sudden unexplained deaths

- Controls: children and adolescents killed in motor vehicle accidents

- Current status: data being collected
Challenges in Case-Control Study

- A major difficulty in conducting a case-control study is the identification of an appropriate control group and the availability (or unavailability) of comparable outcome measures.

- When looking at medical examiner data, there can be much variability in the toxicology screens that are performed.

- Privacy issues can also make it harder to obtain relevant records.

- Difficulty getting a large enough study population to get enough power.
Large Population-based Pharmacoepidemiologic Study

Feasibility study with FDA research contracts:

- Kaiser Foundation Research Institute
  - 6.1 million current members in northern and southern California

- i3 Magnifi Ingenix
  - 12 million enrollees with national representation

- Harvard Pilgrim Healthcare
  - 3.2 million enrollees in 8 plans from the HMO Research Network
  - includes data from six states - MA, MN, WA, CO, GA, NM)

- Vanderbilt University
  - 2.2 million Medicaid recipients in TN and WA
Other Study Options for Risk Characterization

**Echocardiography studies**

- R/O cardiomyopathy, valvulopathy
- Risk factors vs. chronic effects?
- Follow prospective cohort over time?
- Prevalence study of users vs. non-users?
Other Study Options for Risk Characterization

**Cardiovascular PK/PD study**

- Include assessment of heart rate, blood pressure, and QTc during exercise
- Collect PK data for PK/PD correlation
- FDA Guidance: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
Other Study Options for Risk Characterization

**Study lower doses?**

- Characterize lowest effective dose and lowest effective dose producing the maximal therapeutic benefit
- Dose-response relationship at lower doses not known, may have safety advantage
- Possibility of poor metabolizers?
Acknowledgements

- Paul Andreason, MD, Deputy Director, Div Psychiatric Products
- Richardae Araojo, PharmD, DPP Project Management Officer
- Mark Avigan, MD, CM, Director, Div Drug Risk Evaluation
- Stephen Benoit, MD, MPH, Centers for Disease Control
- Allen Brinker, MD, MPH, DDRE Epidemiologist Team Leader
- Madelyn Gould, PhD, MPH, Columbia University
- David Graham, MD, MPH, ODS Associate Dir for Science
- Lisa Jones, MD, DNP Safety Reviewer
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- Judy Racoosin, MD, MPH, DNP Safety Team Leader
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- Lourdes Villalba, MD, DNP Safety Reviewer