Studying Cardiovascular Risk with Drug Treatments of ADHD

Feasibility of Available Study Methods in Children and Adults

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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
  - Wilens TE, Hammerness PG, Biederman J, Kwon A, Spencer TJ, et al. Blood pressure changes associated with medication treatment of adults with attention deficit hyperactivity disorder. *J Clin Psychiatry* 2005; 66(2): 253-259.
- 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.
  - Biederman J, Mick E, Surman C, Doyle R, et al. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit hyperactivity disorder. *Biol Psychiatry* 2005 Dec 19
- 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.

- Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7). *Hypertension*. 2003; 42:1206-1252.

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)

Weisler RH, Biederman J, Spencer TJ, Wilens TE. *CNS Spectrums.* 2005;10(12 *Suppl* 20):35-43.

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).

Samuels JA, Franco K, Wan F, Sorof JM. Effect of stimulants on 24-h ambulatory blood pressure in children with ADHD: a double-blind, randomized, cross-over trial. *Pediatr Nephrol* 2006;21:92-95.

Stowe CD, Gardner SF, Gist CC, et al. 24-Hour ambulatory blood pressure monitoring in male children receiving stimulant therapy. *Ann Pharmacother* 2002;36:1142-9.

Rationale for Safety Concern

- **Very few long-term studies have been done in children:**
  - MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention deficit hyperactivity disorder (ADHD). Arch Gen Psychiatry 1999; 56: 1073-1086.
  - MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24-month outcomes of treatment strategies for attention deficit / hyperactivity disorder. Pediatrics 2004; 113(4): 754-761.
  - Gillberg C, Melander H, von Knorrin A, et al. Long-term central stimulant treatment of children with attention deficit hyperactivity disorder: a randomized double-blind placebo-controlled trial. Arch Gen Psychiatry 1997; 54: 857-864.
  - Wilens T, Pelham W, Stein M, Connors K, Abikoff H, et al. ADHD treatment with once daily OROS methylphenidate: interim 12-month results from a long-term open-label study. J Am Acad Child Adolesc Psychiatry 2003; 42(4): 424-433.
  - Abikoff H, Hechtman L, Klein RG, et al. Symptomatic improvement in children with ADHD treated with long-term methylphenidate and multimodal psychosocial treatment. J Am Acad Child Adolesc Psychiatry 2004; 43: 802-811.
- **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.

FDA Statement July 2005
After Pediatric Advisory Committee

- 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

Estimated Reporting Rates (1992 – 2004) Pediatric Sudden Death (≤ 18 years of age)

Drug	All Age Groups	Pediatric Age Group 0 – 18 Years		
	Total Prescriptions[1]	Pediatric Exposure (p-y)[2]	N[3]	Reporting Rate per 100,000 p-y
Methylphenidate	110,734,000	7,127,432	11	0.2
Amphetamine & Dextroamphetamine	70,699,000	3,817,929	13	0.3
Atomoxetine	9,419,000	601,246	3	0.5

[1] IMS Health, National Prescription Audit *Plus*™, January 1992 through December 2004. Data Extracted April 2005.

[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

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

Zheng Z, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001;104:2158-2163

Estimated Reporting Rates (1992 – 2004) Adult Sudden Death (18+ Years)

Drug	All Age Groups	Adult Age Group 0 – 18 Years		
	Total Prescriptions[1]	Adult Exposure (p-y)[2]	N[3]	Reporting Rate per 100,000 p-y
Methylphenidate	110,734,000	1,764,591	2	0.1
Amphetamine & Dextroamphetamine	70,699,000	1,857,056	6	0.3
Atomoxetine	9,419,000	142,855	4	2.8

[1] IMS Health, National Prescription Audit *Plus*™, January 1992 through December 2004. Data Extracted April 2005.

[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

Age	7-18 years (mean 11.5 years)
Gender	5 male, 3 female
Suspect drug	methylphenidate
Serious adverse events	syncope (1), loss of consciousness (1), dyspnea (1), palpitations / arrhythmia (6), abnormal heart biopsy (1), cardiac arrest (1), stroke (1), QT prolongation (1)
Concomitant medications	none mentioned (2), 1 med (3), 2 meds (3)
Year reported	1999 (0), 2000 (0), 2001 (3), 2002 (1), 2003 (4)

Nonfatal Cardiovascular/Cerebrovascular Serious Adverse Events - Methylphenidate

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

Age	33-75 years (mean 50.6 years)
Gender	6 male, 4 female, 1 not reported
Suspect drug	methylphenidate
Serious adverse events	syncope (2), increased blood pressure / hypertension (3), chest pain (3), heart failure (1), myocardial infarction (3), arrhythmia (2), mitral valve prolapse (1), stroke (1)
Concomitant medications	none mentioned (6), 1 med (2), 2 meds (2), 3 meds (1)
Year reported	1999 (3), 2000 (1), 2001 (2), 2002 (3), 2003 (2)

Nonfatal Cardiovascular/Cerebrovascular Serious Adverse Events - Amphetamine

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

Age	7-17 years (mean 11.4 years)
Gender	15 male, 3 female
Suspect drug	Amphetamine, mixed salts (18)
Serious adverse events	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)
Concomitant medications	none mentioned (6), 1 med (7), 2 meds (1), 3 meds (2), 4 meds (2)
Year reported	1999 (1), 2000 (4), 2001 (4), 2002 (4), 2003 (5)

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?

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