ADHD Stimulant Medication and the Risk of Sudden Cardiac Death

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Attention Deficit Hyperactivity Disorder

- Neurobehavioral disorder marked by one or more of the following:
  - Inattention (poor focus / distractibility)
  - Hyperactivity (excessive motor activity)
  - Impulsivity (no “brakes”)

- Prevalence rates
  - 3-8% of the school-age population
  - Clinically presents more often in boys than in girls (3:1)
  - Three quarters of children retain ADHD symptoms in adolescence, and up to one half as adults

http://www.cdc.gov/ncbddd/adhd/
Molecular Genetics of ADHD

- Specific genes associated with ADHD
  - Dopamine receptor D4 gene (DRD4) on chromosome 11
  - Dopamine transporter gene (DAT1) on chromosome 5
  - D2 dopamine receptor gene
  - Dopamine-beta-hydroxylase gene
  - Possible association of noradrenergic genes
  - Most recently identified: Latrophilin 3 gene (LPHN3), may contribute significantly

- Association suggested between ADHD, parenting characteristics and serotonergic genotypes

Swanson et al, 1998,
Nikolas M et al, Beh and Brain Func 2010 (6) 23

ADHD and Copy Number Variants

- Comparison of genome-wide analysis in children with ADHD (366) and controls (1047)
- CNVs were found twice as often in children with ADHD
- Rate 5X higher in individuals with ADHD and MR
- More than 1/3rd of children with ADHD and intellectual disability carried a large rare CNV
- Significantly enriched for loci previously implicated in patients with ASDs and schizophrenia
- Among the genes spanned by CNV on 16p is NDE1 (nuclear distribution gene E homologue 1) which interacts with DISC1, which is disrupted in schizophrenia

Williams, N, Zaharieva, I, et al Lancet published on line on 9/30/2010
ADHD Treatments

1. Medications
2. Behavioral/Psychological Interventions
3. Educational Interventions
4. Alternative and Complementary Treatments

Catecholamine Reuptake Inhibition Is a Likely MOA of ADHD Drugs
### ADHD Medications

<table>
<thead>
<tr>
<th>Immediate-Release Stimulants</th>
<th>Long-Acting Formulated Stimulants</th>
<th>Non-stimulant</th>
<th>Long-Acting Prodrug Stimulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexmethylphenidate HCl (FOCALIN)</td>
<td>Dexmethylphenidate HCl XR (FOCALIN XR)</td>
<td>Atomoxetine HCl (STRATTERA)</td>
<td>Lisdexamfetamine dimesylate (VYVANSE)</td>
</tr>
<tr>
<td>Methylphenidate HCl (RITALIN)</td>
<td>Methylphenidate HCl CD (METADATE CD)</td>
<td>Guanfacine XR (INTUNIV)</td>
<td></td>
</tr>
<tr>
<td>Mixed salts of a single-entity amphetamine product (ADDERALL)</td>
<td>Methylphenidate HCl LA (RITALIN LA)</td>
<td>Clonidine LA (KAPVAY)</td>
<td></td>
</tr>
<tr>
<td>D-amphetamine (DEXEDRINE)</td>
<td>Methylphenidate transdermal system (DAYTANA)</td>
<td></td>
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<tr>
<td></td>
<td>Mixed salts of a single-entity amphetamine product XR (ADDERALL XR)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>OROS methylphenidate HCl (CONCERTA)</td>
<td></td>
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</tr>
</tbody>
</table>

### Modification of ADHD Medication Impact by Use of Use of Extended Release Systems

- Oral osmotic system
- Timed beads
- Use of pro-drug
- Transcutaneous patch technology
- Delayed disintegration via use of incipients
ADHD

Plasma Profiles Following MPH-IR tid and OROS MPH

- OROS MPH 18mg (n=27)
- MPH – IR 5 mg TID (n=27)

Oral Osmotic Methylphenidate: Heart Rate and Hypertension

- 1 year safety data in children
  - Compared to off-drug baseline
  - Changes in SYS-BP and D-BP of 3.3 and 1.5 mm Hg (P < 0.001)
  - HR increased (3.9 bpm, P < 0.0001)
  - Short term data (previously discussed) did not suggest a change in blood pressure with methylphenidate

- No clear dose-response relationship and no tolerance to pressor effects

- Inverse relationship between baseline vital signs and positive change in vital signs at end point

Mixed Amphetamine Salt XR: Mean (± SD) Heart Rate during Extension Protocol


Adderall XR is contraindicated in patients with symptomatic cardiovascular disease and moderate to severe hypertension. Adderall XR generally should not be used in those with structural cardiac abnormalities.

Use of MAS XR for Up to Two Years in Adults

- Daily doses of mixed amphetamine salts XR from titrated from 20 – 60 mg per day
- Most subjects with a significant V/S abnormality had it at only one visits.
- Seven subjects (of 223 otherwise well adult subjects) discontinued due to a cardiovascular adverse event
  - Hypertension, n=5
  - Palpitation/tachycardia, n=2
  - None of these events was reported as serious
- Several subjects with borderline elevated baseline values exhibited shifts to abnormal values during MAS XR therapy


<table>
<thead>
<tr>
<th></th>
<th>Stimulant Naive</th>
<th>Previously Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change</td>
<td>Mean Final Visit</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>1.62</td>
<td>74</td>
</tr>
<tr>
<td>Sys BP</td>
<td>5.38</td>
<td>102</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>1.00</td>
<td>57.6</td>
</tr>
<tr>
<td>PR Interval</td>
<td>0.46</td>
<td>133</td>
</tr>
<tr>
<td>QRS msec</td>
<td>1.54</td>
<td>82.6</td>
</tr>
<tr>
<td>Qtc msec</td>
<td>5.15</td>
<td>406</td>
</tr>
</tbody>
</table>

*Wigal SB, Lerner MA et al. Postgraduate Medicine, 122(5) Sept 2010*
Transmission of Neuronal Signal is Modulated by the a2A Receptor


Guanfacine and Clonidine Extended Release Agents are Approved for ADHD

- Alpha 2 Adrenergic Receptor Agonists
  - Action: Direct stimulation of post-synaptic sites which support improved working memory and function in the prefrontal cortex
    - Dorsal PFC inhibits distractibility
    - Right Inferior PFC projections involve behavior inhibition
    - Ventromedial PFC regulates emotion
  - New extended release forms, Guanfacine and Clonidine
    - GIR 75% in initial 45 mins Vs. GXR 85% in first 12 hours
    - Tmax: Shift from 3 hour to 6 hours
ADHD and Congenital Heart Disease

- Clinical trials typically screen for serious heart disease and exclude these children from studies.
- Screening of blood pressure and heart rate for safety (EKGs) common.
- Children with many post-operative CHD have increased risk of Sudden Unexpected Death.
- Stimulants generally not recommended.


Audience Participation: ADHD and SCD Question 1

- Should patients with LQTs on beta blockers be allowed to receive stimulant medications for ADHD?
  
  1. Yes
  2. No
  3. Undecided
  4. I defer this decision to my cardiac subspecialty team.
Audience Participation: ADHD and SCD
Question 2 (for pediatric cardiologists)

- Should hemodynamically stable children with an ICD be allowed to receive stimulant medications for ADHD?

- 1. Yes
- 2. No
- 3. I defer this decision to others on my cardiac subspecialty team

Background on the ADHD Controversies

FDA committee votes for warning labels on stimulant drugs

AHA Scientific Statement

Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Medications for Attention Deficit/Hyperactivity Disorder

A Scientific Statement

American Academy of Pediatrics/American Heart Association clarification of statement on cardiovascular evaluation and monitoring of children and adolescents with heart disease receiving medications for ADHD

May 16, 2008

This statement replaces the April 21 news release

Endorsed by the American Academy of Child and Adolescent Psychiatry, the American College of Cardiology, Children and Adults with Attention-Deficit/Hyperactivity Disorder, the National Initiative for Children’s Healthcare Quality and the Society for Developmental and Behavioral Pediatrics

### Baseline Cardiovascular Risks

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate/100,000 Patient – Yr</th>
<th>OROS MPH Serious CV AEs³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden Death¹</td>
<td>Pediatric: 1.3 – 4.6</td>
<td>Adult: 55</td>
</tr>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>MI²</td>
<td>Pediatric: 2.6 – 19.7</td>
<td>Adult: 659</td>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stroke²</td>
<td>Pediatric: 2.7</td>
<td>Adult: 888</td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td>Hypertension²</td>
<td>Pediatric: 4.5</td>
<td>Adult: 32.3</td>
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</tbody>
</table>

²American Heart Association, Heart Disease and Stroke Stats 2006;

### Estimated 1-year (2005) Reporting Rates for Pediatric Sudden Death Children <17 Years of Age

<table>
<thead>
<tr>
<th>Drug</th>
<th>Scripts (Millions)</th>
<th>Pediatric Exposures (Pt Yrs in Thousands)</th>
<th>Deaths</th>
<th>Rate Per 100K Pt-Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>9.9</td>
<td>816</td>
<td>2</td>
<td>0.2</td>
</tr>
<tr>
<td>Amphetamine/Dextroamphetamine</td>
<td>6.9</td>
<td>583</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>3.3</td>
<td>276</td>
<td>4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

FDA Findings: Cardiac Risks for ADHD Class Medications

- Presentation of 6-year data for MTA (Swanson)
  - Minimal difference for heart rate and blood pressure
    - Continuously using stimulants
    - Stimulant naïve
    - Local non-ADHD classroom controls

- Added risk for rare cardiac events difficult to ascertain
  - No recommendation for universal screening (EKG / ECHO)
  - Similar to challenge of identifying risk to children who participate in vigorous exercise (also not recommended for routine screening)

- Consideration of cardiac risk warnings for atomoxetine

- Management of patients with congenital/structural heart disease will often require consultation with pediatric cardiologists


Cardiac Issues and Stimulant Medication Warnings

- Stimulants should generally not be used in children, adolescents and adults with:
  - Serious structural cardiac abnormalities
  - Cardiomyopathy
  - Serious heart rhythm abnormalities
  - Symptomatic cardiovascular disease

- Use with caution in treating patients with underlying medical conditions
  - pre-existing hypertension
  - heart failure
  - recent myocardial infarction, or ventricular arrhythmia
**Stimulant Class Cardiac Warnings**

- Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems.
- Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses in ADHD.
- Physicians should take a careful patient history, including family history, and physical exam, to assess the presence of cardiac disease.
- Patients who report symptoms of cardiac disease such as exertional chest pain and unexplained syncope should be promptly evaluated.
- Use with caution in patients whose underlying medical condition might be affected by increases in blood pressure or heart rate.

**Amphetamine Black Box Warning: Important Safety Information**

- Amphetamines have a high potential for abuse.
- Administration of amphetamines for long periods of time may lead to drug dependence.
- Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic uses or distribution to others and the drugs should be prescribed sparingly.
- Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events.
ADHD in Children with Congenital Heart Disease

- ADHD symptoms may be more prevalent in children with CHD concerns
  - Abnormal attention scores in 45% with children with CHD
  - Abnormal hyperactivity scores in 39% of children with heart disease (parents and teacher ratings)
- Increased risk with specific congenital cardiac issues
  - > 2/3 with hypoplastic left heart syndrome
  - 50% of children with TAPVR
  - Cardiac issues associated with 22q11 microdeletion caused ADHD 35% to 55% of children


Methods

Parents

SNAP-IV Questionnaires

Counselors
Prevalance of Attention Deficit/Hyperactivity Disorder Symptoms in Patients With Congenital Heart Disease

Children with Congenital Heart Disease (n=64)
- Age: 8-18 yrs (mean 13.4 ± 2.6 yrs)

Disorders of Subjects
- VSD (10)
- Coarc (14)
- AS (5)
- ASD (4)
- TOF (6)
- TGA (4)
- HLH (5)
- Truncus (4)
- SV (7)
- MR (4)
- TAPVC (2)
- PS (3)
- Pul Atresia (3)

Cyanotic abnormalities: 31
Acyanotic abnormalities: 33
Severe CHD: 38
Mild to Moderate CHD: 26

ADHD Positive Comparison Group (n=75)
Ages 10-12 yrs old

ADHD Negative Comparison Group (n=41)
Ages 10-12 yrs old

Prevalence of ADHD

9.3% vs 5.0%
p = 0.05

Risk Factors for ADHD

Cyanosis/Acyanosis

Severity of Cardiac Disease

* No significance was found

Inattention

**p < 0.001**
Hyperactivity/Impulsivity

![Graph showing average Parent SNAP-IV Rating for ADHD Positive, CHD, and ADHD Negative groups with p < 0.005.]

The Patient History Prior to Stimulant Use

- History of fainting or dizziness (particularly with exercise)
- Seizures
- Rheumatic fever
- Shortness of breath or noticeable change in exercise tolerance
- Chest pain, palpitations, increased heart rate, or extra or skipped heart beats
- History of high BP, significant heart murmur or disease

Vetter VL, Elia J, et al DOI:10.1161/CIRCULATIONAHA.107.189473
Family History Prior to Stimulant Use

- Sudden or unexplained death in young
- SCD or “heart attack” or need for CPR if <35 years of age or during exercise or syncope requiring resuscitation
- Cardiac arrhythmias, HCM or other cardiomyopathy
- LQTS, short-QT syndrome, or Brugada syndrome
- WPW or similar abnormal rhythm conditions.
- Marfan syndrome


Physical Examination Findings Mandating Referral

- Abnormal heart murmur
- Other cardiovascular abnormalities, hypertension or irregular or rapid heart rhythm
- Physical findings suggestive of Marfan syndrome

Significant ECG Abnormalities Needing Referral

- Left or right ventricular hypertrophy
- Left axis deviation or right axis deviation, especially 8 y of age
- Right atrial enlargement and right axis deviation
- Right ventricular conduction delay and right axis deviation
- Wolff-Parkinson-White anomaly or pattern (WPW)
- Second- and third-degree atrioventricular block
- Right BBB block, left BBB block, i-v conduction delay 0.12 s in patients 12 y of age (0.10 s in patients 8 y of age)
- Prolonged QTc 0.46 s
- Abnormal T waves with inversion V5, V6; bizarre T-wave morphology, findings suggesting ischemia or inflammation
- Atrial, junctional, or ventricular tachyarrhythmias, including frequent premature atrial contractions or premature ventricular contractions

Stimulants are Option for Non-responsive ADHD

- CHD that is not repaired or repaired but without current hemodynamic or arrhythmic concerns
- CHD considered stable by the patient's pediatric cardiologist
- Use stimulants with caution after other treatments
  - Heart condition associated with SCD
  - History of an arrhythmia requiring CPR or resuscitation cardioversion or defibrillation
  - History of an arrhythmia associated with death or SCD or previous aborted SCD
  - Clinically significant arrhythmia not treated or controlled
  - QTc on ECG 0.46 seconds.
  - Heart rate or BP > 2 S.D. for age
Audience Participation: ADHD and SCD
Question 3

- Should competitive athletes with ADHD who receive stimulant medications be encouraged to receive a pre-participation comprehensive cardiac evaluation (EKG and ECHO)?

1. Yes
2. No
3. Undecided
4. I defer this decision to my cardiac subspecialty team

Alternative Screening Strategies for Cardiac Abnormalities in Children with ADHD

Denchev, P, Kaltman J, MD; Michael Schoenbaum, et al; CIRCULATION 109.901256
ADHD and Universal ECGs: Expected Incremental Cost-effectiveness (vs. Current Practice)

- Study models heart disease screening at 7 and ADHD treatment from age 7 to 17
- Paper assumes that stimulants for ADHD increase the risk of SCD in children with HD by 10% over the baseline SCD rate
- Analysis based on long list of assumptions / parameters (cost of cardiac studies, consultations, chance of medication use, costs of meds, discontinuation rates over time)

Denchev, P, Kaltman J, MD; Michael Schoenbaum, et al; CIRCULATION 109.901256

Conclusions - Adding ECG screening Hx and PE as a PreRx Screening Has Borderline Cost-effectiveness for Preventing SCD

- Strategy 2 = $39 300 per quality-adjusted life-year
- Strategy 3 = $27 200 per quality-adjusted life-year
- Both strategies would avert 13 SCDs per 400 000 children seeking stimulants for ADHD
- Cost per saved life:
  - $1.6 million per life for strategy 2
  - $1.2 million per life for strategy 3
- There is substantial uncertainty surrounding several of the assumptions
- When this uncertainty is taken into account, adding ECG to H&P has a 55% probability of being cost-effective at or below the target of $50 000/QALY relative to current practice
Pediatric Cardiac Risk Assessment Before the Use of Stimulant Medications

A joint position statement
- Canadian Paediatric Society
- Canadian Cardiovascular Society
- Canadian Academy of Child and Adolescent Psychiatry

“For patients with known CHD or arrhythmias, certain disorders are known to be associated with an increased risk of sudden death. Such patients should already be under the care of a cardiologist. Because there is no compelling evidence that ADHD medications raise the risk of sudden death even further, initiation of ADHD medication should be primarily at the recommendation of an ADHD specialist, although discussion of treatment choices with the responsible cardiologist is appropriate.”

Paediatr Child Health 2009;14(9):579-85 Reference No. CPS 2009-02

Canadian Joint Statement – Should All ADHD Patients See a Cardiologist?

“For patients with newly identified risk factors for coexistent cardiac disease, as per the proposed checklist, consultation with a heart specialist should be sought, regardless of whether ADHD medication will be prescribed. This would also be true in the non-ADHD patient.”

“There is currently no evidence to support routine consultation with a cardiologist before the start of ADHD medication.”

Paediatr Child Health 2009;14(9):579-85 Reference No. CPS 2009-02
Cardiac Deaths / Events linked to ADHD in Florida

- Retrospective cohort study (July 1994 - June 2004) of Florida Medicaid claims data cross-linked to Vital Statistics Death Registry data

- Data on all youth 3 to 20 years old who were newly diagnosed with ADHD
  - 55,383 patients with new ADHD
    - 32,807 of these with claims for stimulants
    - 22,576 without claim

- Preexisting heart disease = presence of any inpatient or outpatient claim within 6 months before first ADHD diagnosis or first stimulant claim

Winterstein A, Tobias Gerhard, T et al; PEDS Vol 120, # 6, 12/2007 e1494 - 1501

Cardiac Deaths / Events linked to ADHD in Florida

- Stimulants associated with increased ED and office visits for cardiac symptoms

- Rates of cardiac hospitalizations and fatalities were small and similar to national background

- 124,932 person-years of observation
  - 73 youth died
  - 5 died because of cardiac causes

- No cardiac death occurred during 42,612 person-years of stimulant use

Winterstein A, Tobias Gerhard, T et al; PEDS Vol 120, # 6, 12/2007 e1494 - 1501
Summary:

- ADHD is a common neurobehavioral disorder of childhood
- Cardiovascular parameters are impacted by ADHD treatments
- Many children with CHD have symptoms of ADHD
- Screening of children with ADHD for cardiac concerns is recommended, universal use of ECGs prior to the initiation of ADHD medication is controversial