



Psychotropic & Stimulant Medications: Cardiovascular Drug Safety in Children

Cardiac Safety Research Consortium

Pediatric Thinktank

FDA Headquarters

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Overview

- **What are the CV risks conferred by psychotropics?**
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- **Are there populations at greater CV risk?**
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- **Are there risks that need further evaluation?**
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- **Are there any CV benefits from these meds?**

STIMULANTS – HR, BP

	Mean Group Change	Outliers
HR	↑ Δ 3-10 bpm	$\Delta \geq 25$ bpm / > 110 bpm
SBP	↑ Δ 3-4 mmHg	$\Delta \geq 20$ mmHg/ > 130 mmHg
DBP	↑ Δ 1-14 mmHg	$\Delta \geq 10$ mmHg/ > 100 mmHg

Are increases in HR and BP related to increased sympathetic activity?

STIMULANTS – EKG

Clinical Trials

MPH and AMPH

pl.c (4wks) studies

Open studies (3-24mos)

No QRS changes for most children

0.1% Slight (QTc) increases – none >500msec

2% of subjects developed rhythm and conduction problems (ectopic atrial rhythm, complete or incomplete RBBB and left anterior hemiblock)

1 subject developed RBB and prolonged QT that resolved when AMPH was discontinued

1 subject had a prolonged QT interval that resolved when AMPH was discontinued

Adult MPH Overdose

(40-1500mg; 120mg median dose) (Hill 2010;48;342)

No arrhythmias

No differences in HR, QRS, QT, QTc in subjects vs. controls

QT Interval Duration and Dispersion (MPH)

(Igenli 2007;24)

QT dispersion reduced during acute administration

Animal Study (MPH - 3, 10 and 30mg/kg)

(Wakamatsu 2009;59;128)

No arrhythmias

No significant changes noted except for QT shortening (14%) at 30mg/kg dose

STIMULANTS – Sudden Cardiac Death

Clinical Trials

None

Case Reports

MPH (Daley 2008:1408)
MHP + clonidine (Swanson 1995:5:301)
MPH + clonidine + fluoxetine (Swanson 1995:5:301; Cantwell 1997;36:539; Sallee 2000:10;27)

Retrospective Cohort Study

73 deaths

Medical Claims Data

5/73 were patients tx with stimulants

10yrs /125,000 person-yrs/ ages 3-20

None of the deaths occurred during tx.

(Winterstein 2007:e1494)

FDA Data (AERS 1999-2003)

25 deaths (19 in children - 2/3 with structural cardiac abnormalities)

12 cases in children treated with mixed AMPH salts

7 cases reported with mph

Case Control Study


10 subjects from 564 cases of unexplained SCD

US Mortality Data 1985-1996 /Ages 7-19

were taking stimulants while only two subjects from comparison group (died as passengers in MVA)

(Gould 2009;166;992)

Stimulants –Populations at greater CV risk?

	Adults / Animal Studies	Children with ADHD
Comorbid Anxiety	Increases risk of SCD Decreases Variability in HR Increases QT variability	30%
Comorbid Mood Disorders	Cardiac deaths in melancholic adult patients 8X > general population (Malzberg 1937)	25%
Genetic Variants 	CES: ENCODES FOR CARBOXYLESTERASE – METABOLIC DEACTIVATION OF MPH Single nucleotide mutation in exons 4 and 6 result in loss of function of this enzyme	
Drug Interactions AMPH is a substrate of CYP2D6 – SSRI's inhibit this enzyme potentially increasing AMPH levels	Increased amph conc reported in rat brains pretreated with fluoxetine	Cardiac arrest in 9 yo with ADHD, OCD and TS tx with MPH, clonidine and fluoxetine over 10 months. CYP2D gene variant was found (Sallee 2000;10:27) 13 year old tx with sertraline for OCD develops AV nodal re-entrant tachycardia 5 days after starting tx with amph. Same thing occurred with MPH

STIMULANTS- UNKNOWN CV RISKS

Long-Term Exposure	Does continuous tx with sympathomimetics present a risk of HPT or other CV risks?
Anesthesia	<p>8 yo tx with MPH for 2 years and clonidine for 3 mos died after receiving general anesthesia for hand surgery</p> <p>A 10-yo tx with MPH for 4 years undergoing general anesthesia for laser therapy of a facial hemangioma was resuscitated after developing severe bradycardia followed by asystole.</p> <p>Does long-term administration of stimulants result in depletion of NE and DA storage, which can result in a blunted sympathetic response, leading to a lack of appropriate tachycardic response during anesthesia?</p>
Teratogenicity	Intra-uterine exposure in albino mice led to delay of histo-differentiation of the myocardium resulting in incomplete maturation of cardiac muscle

ADHD RISKS

What this means for children and young adults

- ↑ Repeated grades
- ↑ School suspensions
- ↓ High school graduation
- ↓ College enrollment
- ↑ Dating partners
- ↓ Length of relationships
- ↑ Became parents
- ↑ Contracted STDs
- ↑ Work firings
- ↓ Acquaintances
- ↓ Close friends
- ↑ Social problems
- ↑ Smoking rate
- ↑ Smoking age of onset
- ↑ Difficulties quitting smoking
- ↓ Obtaining credit
- ↑ Amount of debt
- ↑ Owe money
- ↓ Have a savings account
- ↑ Difficulties paying bills
- ↑ Driving with suspended license
- ↑ Traffic violations
- ↑ Hit-and-run crashes
- ↑ Slower/variable driving reactions
- ↑ Steering variability
- ↑ Scrapes
- ↑ Crashes against barriers
- ↓ Traffic rule compliance

(Age ≤ 25)

ANTIDEPRESSANTS /ANTIPSYCHOTICS

	DIRECT CV EFFECTS	INDIRECT CV EFFECTS
Fluoxetine (MDD, OCD) Escitalopram (MDD) Sertraline (OCD) Luvox (OCD)	No significant effects	Drug Interactions In-Utero Exposure Paroxetine - Pulmonary Hypertension of the Newborn Overdose
Risperidone (SCZ; BPD) Quetiapine (SCZ; BPD) Aripiprazole (SC; BPD) Olanzapine (SCZ)	QT Prolongation SCD Ventricular Arrhythmia	Schizophrenia Weight Gain Metabolic Syndrome



Thanks for your attention!