National Resource Center on AD|HD
A Program of CHADD

Ask the Expert: Children, Medications, and Heart Safety: A Tale of ADHD and Public Health

Sue Visser, MS

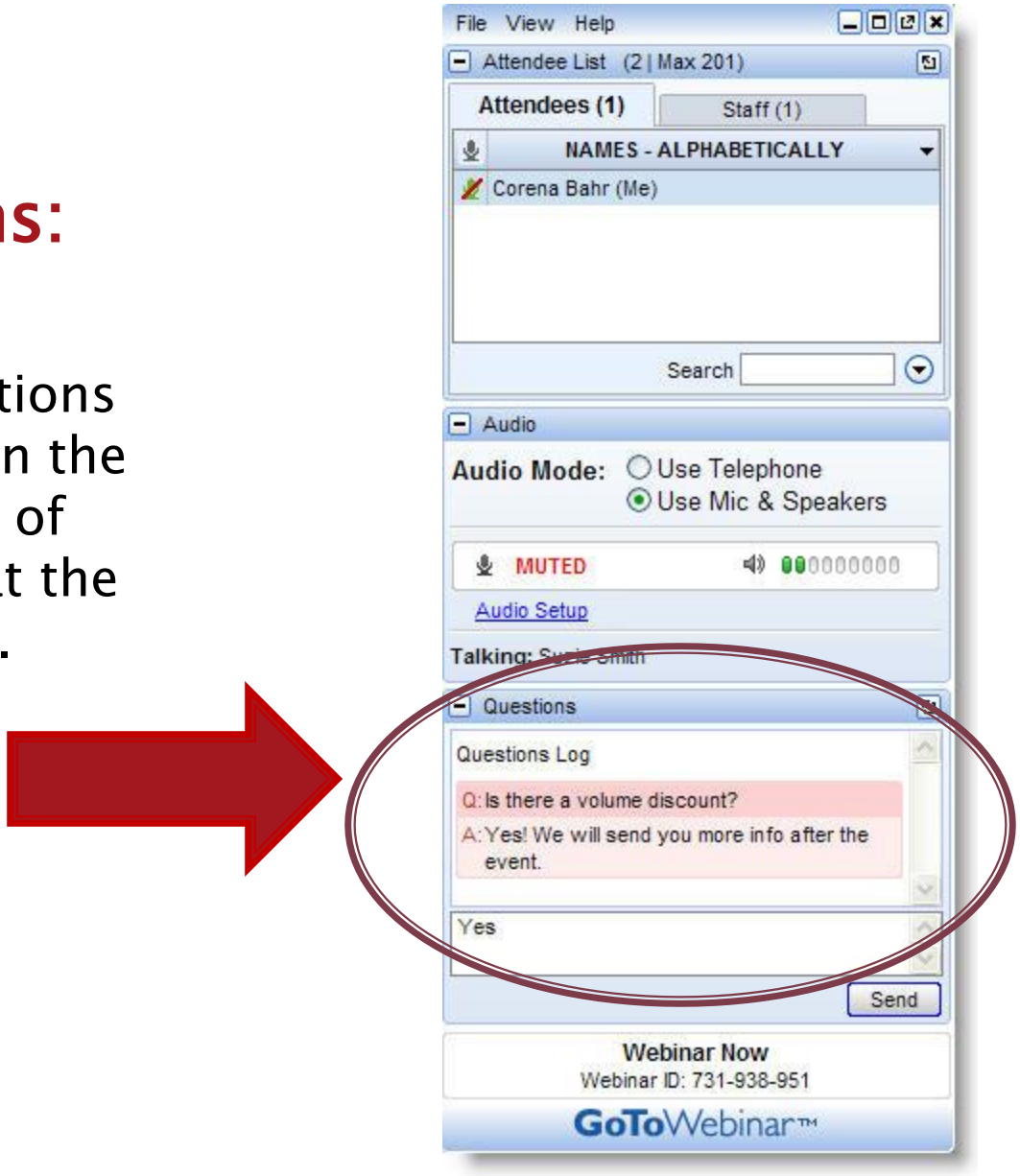
Lead Epidemiologist, Child Development Studies Team
National Center on Birth Defects and Developmental Disabilities
CDC

National Public Health Week 2013
April 4, 2013

National Center on Birth Defects and Developmental Disabilities
Division of Human Development and Disabilities

To Ask Questions:

Please type your questions for today's expert in the "Questions" window of your control panel at the right of your screen.



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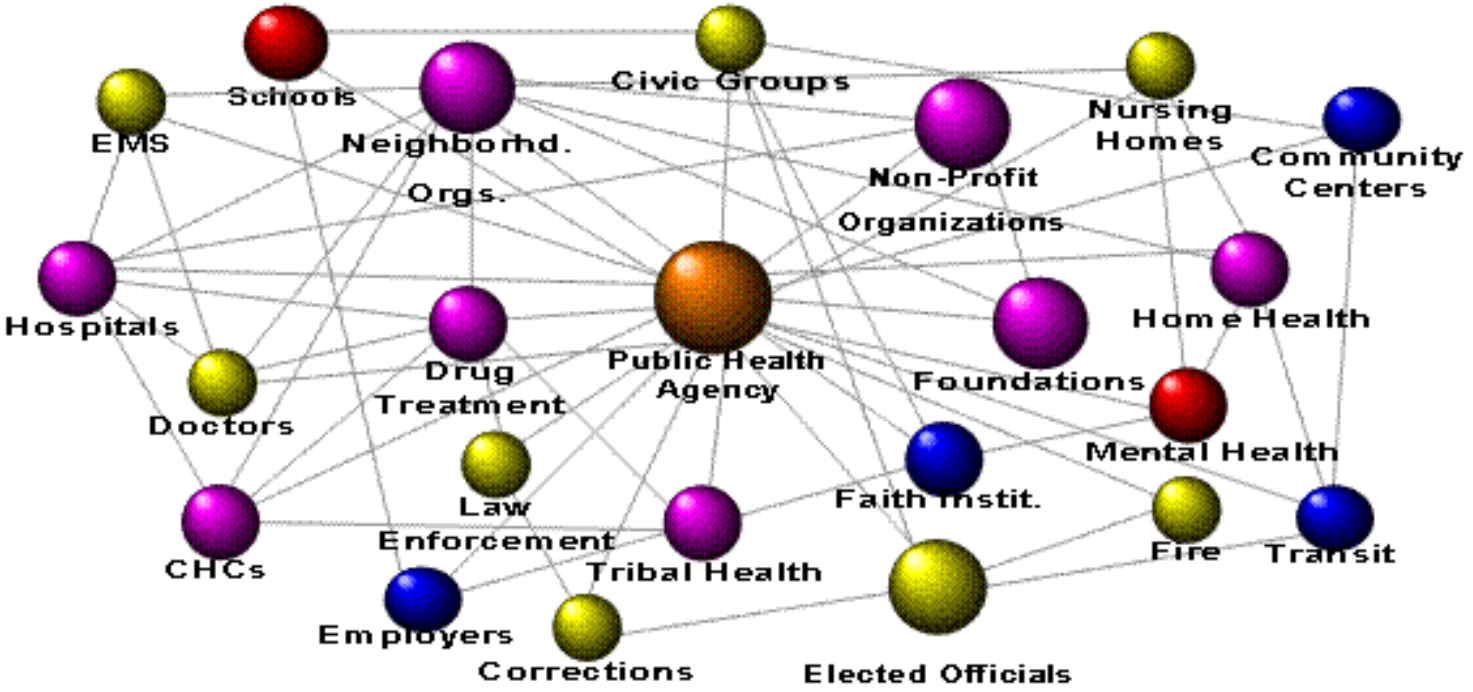
Happy National Public Health Week!
10 Essential Services of Public Health

1) Monitor health status to identify and solve community health problems.
2) Diagnose and investigate health problems and health hazards in the community.
3) Inform, educate, and empower people about health issues.
4) Mobilize community partnerships and action to identify and solve health problems.
5) Develop policies and plans that support individual and community health efforts.
6) Enforce laws and regulations that protect health and ensure safety.
7) Link people to needed personal health services and assure the provision of health care when otherwise unavailable.
8) Assure competent public and personal health care workforce.
9) Evaluate effectiveness, accessibility, and quality of personal and population-based health services.
10) Research for new insights and innovative solutions to health problems.

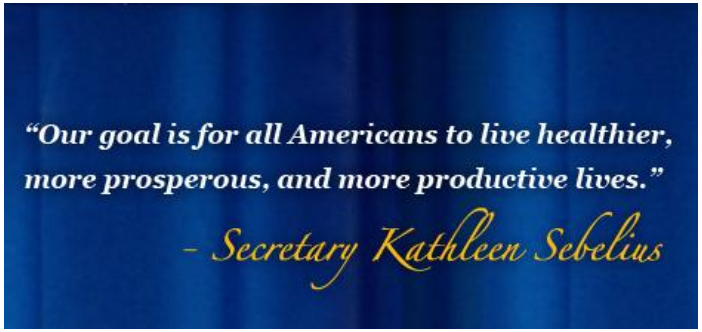
http://www.cdc.gov/nphpsp/essentialservices.html

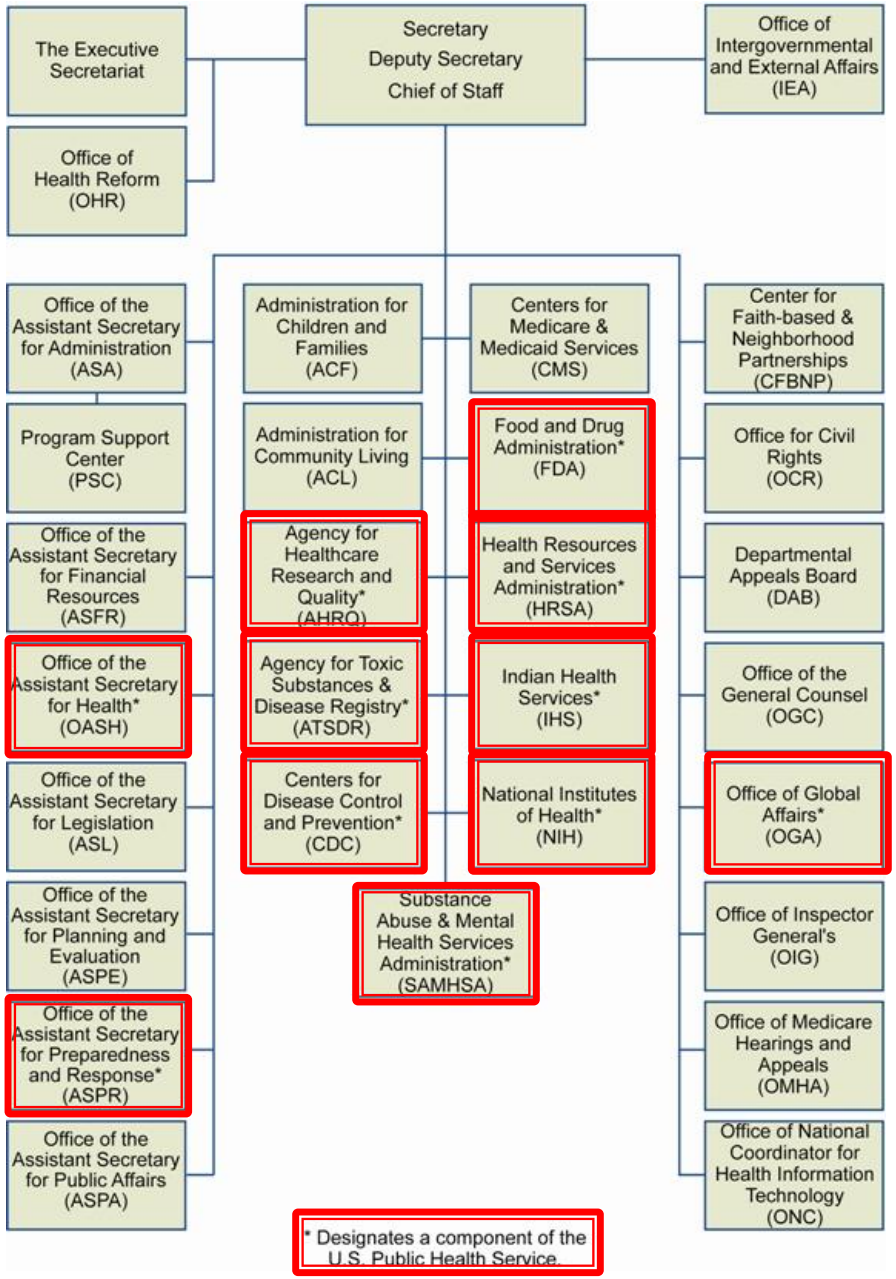
The Public Health System



*Citations and references - Myriad Pro, 11 pt

Department of Health and Human Services





http://www.hhs.gov/secretary/about/appendixa.html

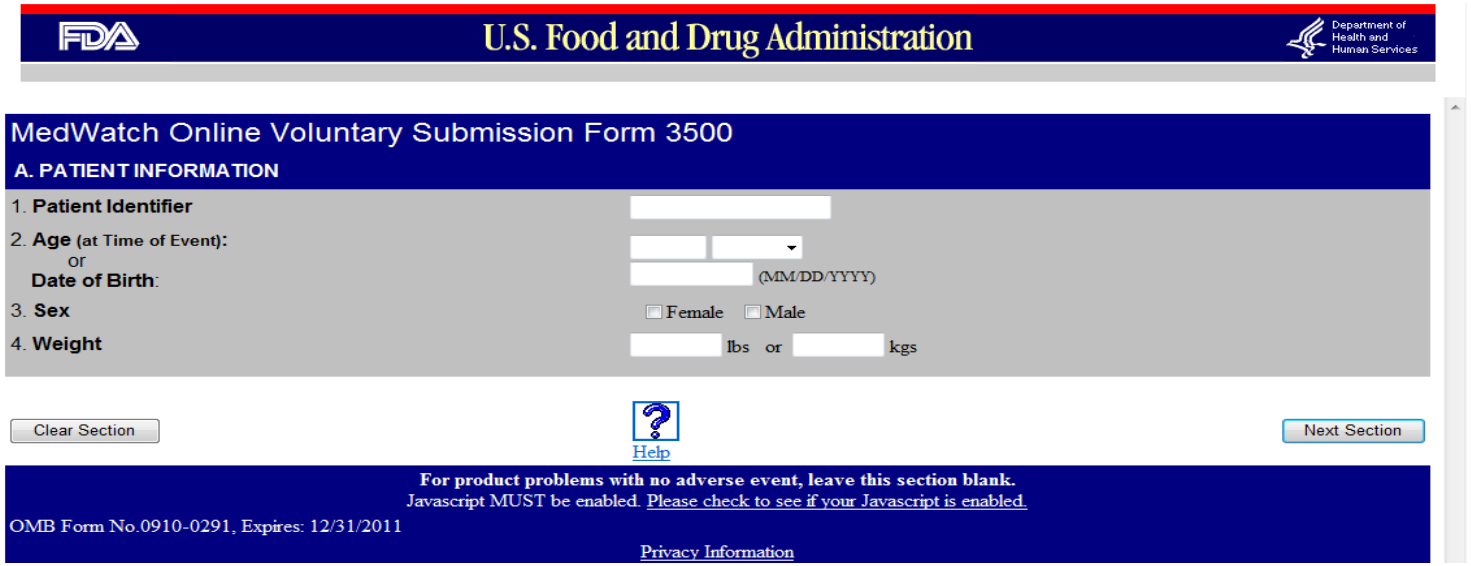
FDA Drug Safety Announcement

November 1, 2011

- Health care professionals should take special note that:
  - Stimulant products and atomoxetine should generally not be used in patients with serious heart problems, or for whom an increase in blood pressure or heart rate would be problematic.
  - Patients treated with ADHD medications should be periodically monitored for changes in heart rate or blood pressure.
- Patients should continue to use their medicine for the treatment of ADHD as prescribed by their healthcare professional.

http://go.usa.gov/2GcP

FDA's MedWatch Adverse Events Reporting System



- ADHD Medication Use and:
  - Arrhythmia
  - Cardiac Arrest
  - Stroke (Cerebrovascular Accident)
  - Myocardial Infarction
  - Sudden Death

Suspicious Adverse Event
Sample: Actual Event

- *"A pathologist reported a 13 year old male died during football practice secondary to a suspected cardiac arrhythmia. The autopsy revealed a hypertrophied and enlarged heart with anomalies of the tricuspid valve. Methylphenidate was present within a therapeutic range. It is unknown how long the patient had been taking the medication."*

FDA's
MedWatch Adverse Events Reporting System

- **Cardiovascular incident or stroke**
  - 54 total
- **Sudden Death**
  - 25 total, 19 pediatric
- Cardiac arrest, MI, and sudden unexplained death were among the top 50 adverse events reported after use of amphetamines and methylphenidate

*Citations and references - Myriad Pro, 11 pt

FDA Committees Assembled

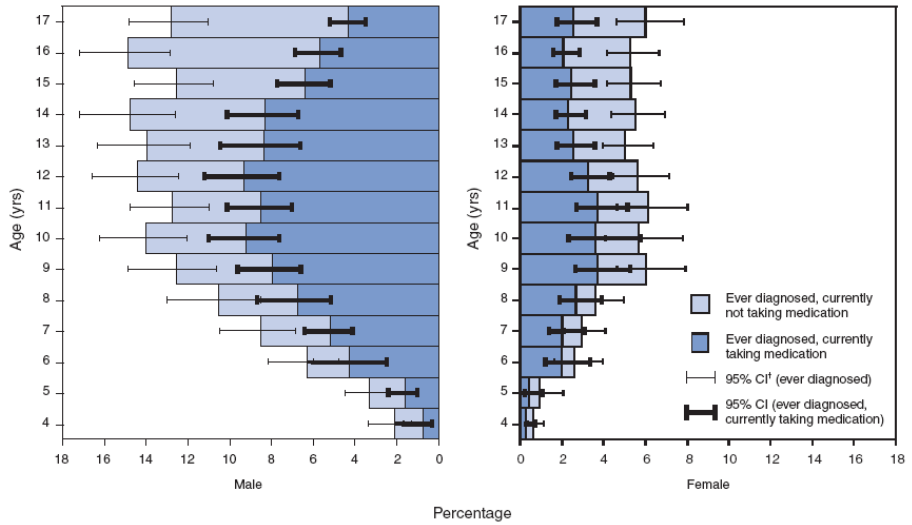
- FDA: "Consider the feasibility of various epidemiologic approaches to further investigate the safety signal and to address specific methodological considerations"
  - Drug Safety and Risk Management Committee
  - Pediatric Advisory Committee

- Research question: **Do ADHD medications cause cardiovascular incident or sudden death?**
  - What would we expect the rate of these adverse events to be in the overall population of children?
  - Is the prevalence of these adverse events higher among children taking ADHD medications?

Epidemiology of ADHD and Adverse Events

- How many American children have ADHD?
  - How many of these are taking ADHD medication?

FIGURE 1. Percentage of children aged 4–17 years ever diagnosed with ADHD,* by age, sex, and medication treatment status — United States, 2003



- How frequently do we see these adverse events among children?
  - Among children with ADHD?
    - Among children taking ADHD medication?
      - .2-.5 per million pediatric prescriptions for amphetamines and methylphenidate, separately.

Centers for Disease Control and Prevention. Prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder - United States, 2003. MMWR 2005;54:[842-847].

Advisory Committee Actions
February–March, 2006

- Motion to vote on the recommendation of a Black Box for all stimulant medications approved to treat ADHD
  - Drug Safety: 8–7–1
  - Pediatric: Not Recommended
- Motion to vote on the recommendation of a patient's guide for all medications approved to treat ADHD
  - Drug Safety: 15–0–1

FDA "Black Box" Warning Label

The Food and Drug Administration (FDA) requires the following "black box" warning on all methylphenidate drugs, including Ritalin, which means that medical studies indicate Ritalin carries a significant risk of serious, or even life-threatening, adverse effects.

FDA Asks Attention-Deficit Hyperactivity Disorder (ADHD) Drug Manufacturers to Develop Patient Medication Guides

FDA has directed the manufacturers of all drug products approved for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) to develop patient Medication Guides to alert patients to possible cardiovascular risks and risks of adverse psychiatric symptoms associated with the medicines, and to advise them of precautions that can be taken.

- FDA Press Release (issued February 21, 2007)
- Advisory Committee Transcripts
  - Drug Safety and Risk Management Advisory Committee, February 9, 2006
  - Pediatric Advisory Committee, March 22, 2006

Drugs

Note: This page links to PDF files which require the free Adobe Acrobat Reader.

Adderall (mixed salts of a single entity amphetamine product) Tablets	Medication Guide	Label
Adderall XR (mixed salts of a single entity amphetamine product) Extended-Release Capsules	Medication Guide	Label
Concerta (methylphenidate hydrochloride) Extended-Release Tablets	Medication Guide	Label
Daytrana (methylphenidate) Transdermal System	Medication Guide	Label
Desoxyn (methamphetamine hydrochloride) Tablets	Medication Guide	Label
Dexedrine (dextroamphetamine sulfate) Spansule Capsules and Tablets	Medication Guide	Label
Focalin (dexmethylphenidate hydrochloride) Tablets	Medication Guide	Label
Focalin XR (dexmethylphenidate hydrochloride) Extended-Release Capsules	Medication Guide	Label
Metadate CD (methylphenidate hydrochloride) Extended-Release Capsules	Medication Guide	Label
Methylin (methylphenidate hydrochloride) Oral Solution	Medication Guide	Label
Methylin (methylphenidate hydrochloride) Chewable Tablets	Medication Guide	Label
Ritalin (methylphenidate hydrochloride) Tablets	Medication Guide	Label
Ritalin SR (methylphenidate hydrochloride) Sustained-Release Tablets	Medication Guide	Label
Ritalin LA (methylphenidate hydrochloride) Extended-Release Capsules	Medication Guide	Label
Strattera (atomoxetine hydrochloride) Capsules	Medication Guide	Label

Wall Street Journal, 2/10/2006

Strong ADHD Drug Alerts Are Urged

FDA Might Not Heed Advice Of Split Advisory Committee About Heart-Risk Labeling

By Anna Wilde Mathews And Scott Hensley

WASHINGTON—In a surprise move, a Food and Drug Administration advisory committee voted to recommend that stimulant drugs widely prescribed for attention-deficit hyperactivity disorder carry strong "black box" warnings about potential cardiovascular risks.

The 8-7 vote, with one abstention, focused on drugs including **Shire** PLC's Adderall, a form of amphetamine, **Novartis** AG's Ritalin, generically sold as methylphenidate, and **Johnson & Johnson**'s Concerta, a long-acting version of methylphenidate. The FDA had asked the committee to look only at how it should study the issue in the future to determine the possible dangers of the drugs, and the agency may choose not to follow the advice of the committee.

The warning proposed by a member of the committee would say that the drugs have been associated with increases in blood pressure and heart rate, which potentially can result in increased risk of heart attack, stroke or sudden death. The data showing such dangers were limited, and the rate of serious problems appeared low.

A black-box warning is the most stringent the FDA can apply to a drug and sends a clear signal to doctors that they should think hard before prescribing a medicine. That in turn can depress sales of the drugs, as recently happened when such warnings were added to common antidepressants after they were associated with increased risk of suicide in children.

Makers of the ADHD drugs said they would work with the agency. A spokesman for Shire said the company supports Adderall's current labeling but is "open to working with the FDA." A spokeswoman for J&J said the company "supports the FDA in their efforts to ensure the appropriate labeling" for all ADHD medications. Novartis, which makes Ritalin, said its review of a company safety database stretching back 50 years doesn't appear to show "an increase in cardiovascular events" in the context of expected rates, but the company said it would "work with the FDA to do what is in the best interest of patients with ADHD."

Use of ADHD drugs has grown rapidly in the U.S. Traditionally, they are prescribed largely to children and teens, but a growing number of adults

Please Turn to Page A14, Column 3

Rx ADHD

U.S. sales for leading medicines prescribed for attention-deficit hyperactivity disorder

DRUG/MAKER	2005 SALES*
Adderall Shire PLC	$1,160.3 million
Concerta Johnson & Johnson	929.4
Strattera Eli Lilly & Co.	742.1
Ritalin Novartis AG	174.1
Metadate UCB	100.2
Methylphenidate Various (generic)	81.1
Focalin Novartis AG	65.6

*Sales reflect all formulations of each brand, where applicable

Source: Wolters Kluwer Health

FDA Action

- Rationale
  - BP & HR increases observed in patients treated with methylphenidate, amphetamine, and atomoxetine
  - Reports of serious cardiovascular events with use of ADHD drugs

- FDA & AHRQ sponsored studies of serious cardiovascular events and ADHD drug use
  - 2 pediatric studies
  - 2 adults studies

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.
Learn and Live.

Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs: A Scientific Statement From the American Heart Association Council on Cardiovascular Disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing

Victoria L. Vetter, Josephine Elia, Christopher Erickson, Stuart Berger, Nathan Blum, Karen Uzark and Catherine L. Webb

Circulation 2008;117;2407-2423; originally published online Apr 21, 2008;
DOI: 10.1161/CIRCULATIONAHA.107.189473
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

"The consensus of the committee is that it is reasonable and useful to obtain ECGs as part of the evaluation of children being considered for stimulant drug therapy. We recognize that there are no clinical trials to inform us on this topic and that there is variance in opinion on this topic."

*Citations and references - Myriad Pro, 11 pt

Gould et al., 2009

- Matched case-control study based on retrospective interviews and medical record review
- Stimulant use in healthy US children who died suddenly vs. stimulant use in children who died as passengers in a motor vehicle accident

- Key Findings
  - 564 healthy children who died suddenly: 10 were taking stimulants
  - 564 healthy children who died in a motor vehicle accident: 2 were taking stimulants
  - Conclusion: There may be an association between the use of stimulants and sudden death in healthy children

- FDA: *"This study should not serve as a basis for parents to stop a child's stimulant medication. Parents should discuss concerns about the use of these medicines with the prescribing healthcare professional."*

Gould MS, Walsh BT, Munfakh JL, Kleinman M, Duan N, Olfson M, Greenhill L, Cooper T: Sudden death and use of stimulant medications in youth. Am J Psychiatry (published online June 15, 2009; doi:10.1176/appi.ajp.2009.09040538)

Cooper et al., 2011

- Review of administrative record/claims data
- Conducted with 1,200,438 children and young adults (aged 2-24 years)
  - 2,579,104 person-years of follow-up
- Key Findings
  - 7 serious cardiovascular events in current ADHD medication users
    - 4 strokes; 3 sudden cardiac deaths
    - All 7 occurred in Medicaid patients
  - No association of serious cardiovascular events with ADHD med use
    - Adjusted hazard ratio 0.75 (95% confidence limits: 0.31-1.85)
  - Rate of 1.87 events per 100,000 person-years (very small absolute risk)
- FDA: *"The results were not consistent with the 7-fold increase in sudden death reported in a case-control study published by Gould et al., but a small to modest increase in risk cannot be excluded."*

Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med 2011.

Habel et al., 2011

- Reviewed administrative records of over 440,000 adults (25-64 y)
  - Study 1: evaluated heart attacks and sudden cardiac deaths
  - Study 2: assessed strokes
- Key findings
  - 806,182 person-years of follow-up
    - 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke
  - The adjusted rate ratio of serious cardiovascular events for current use vs. nonuse of ADHD medications was 0.83 (95% CI, 0.72-0.96)
  - Conclusion: Among young and middle-aged adults stimulant use was not associated with an increased risk of serious cardiovascular events.

Habel LA, Cooper WO, Sox CM, et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. JAMA[18] [19] 2011 (published online December 12, 2011; doi: 10.1001/jama.2011.1830).

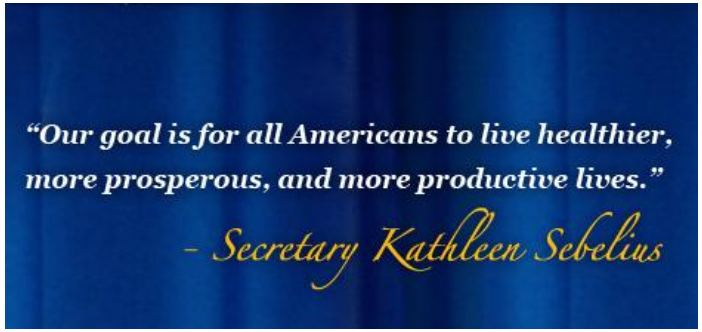
FDA Recommendations

- *FDA recommendations for the use of medications to treat ADHD have not changed. Health care professionals should continue to take special note that:*
  - *Stimulant products and atomoxetine should generally not be used in patients with serious heart problems, or for whom an increase in blood pressure or heart rate would be problematic.*
  - *Patients treated with ADHD medications should be periodically monitored for changes in heart rate or blood pressure.*
- *Patients should continue to use their medicine for the treatment of ADHD as prescribed by their healthcare professional.*

http://www.fda.gov/drugs/drugsafety/ucm277770.htm

Conclusions

- Working to protect the public's health is a cross-Public Health system endeavor!
- In this case:
  - Voluntary Adverse Event Reporting
    - Clinicians
  - Committee and Hearing Participation
    - Clinicians and the public
  - Data Collection and Epidemiology
    - HRSA & CDC
  - Research
    - FDA, AHRQ, NIH
- Many other systems may have passively or directly influenced this process
- Parents and families are key stakeholders and participants of our work!



Thank you!

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Follow me on Twitter – @VisserCDC

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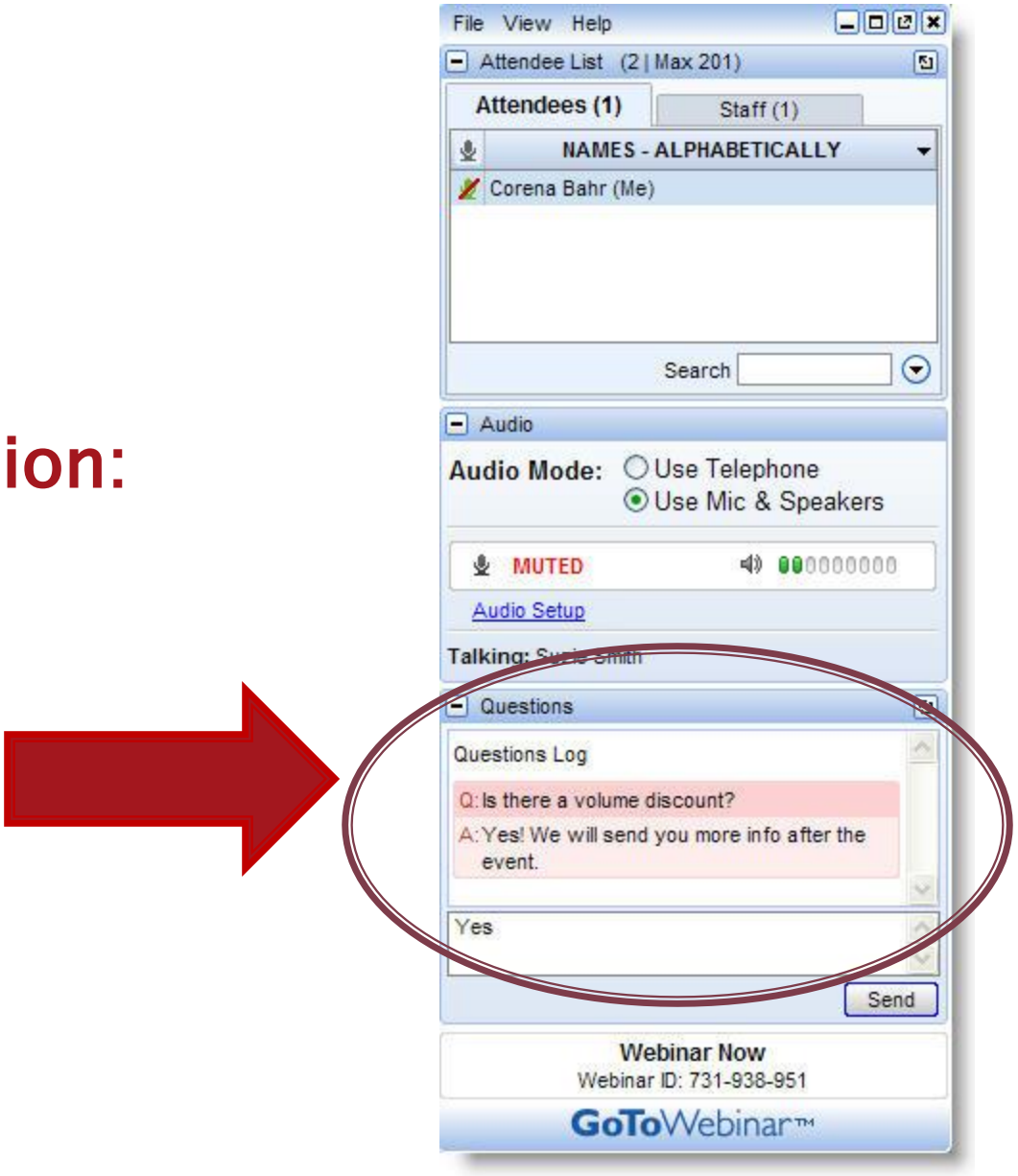

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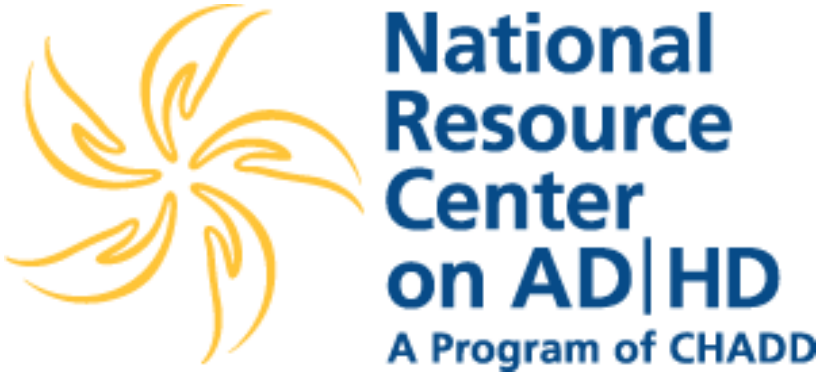

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