

# The cardiac side effects of stimulants, anti-psychotics and anti-depressants in children

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# Why do we worry about the cardiac effects of these medications?

- The major concern surrounds treatment of ADHD
- Growing issue in the UK
- Frequent reason for referral to paediatric cardiologists for assessment
- I am therefore going to focus much of this discussion on medication for ADHD



# Frequent referral letters...

- Dear Doctor, please review this patient in your outpatient clinic. I have diagnosed them with Attention Deficit Disorder and wish to commence medication. As per our current practice I am referring him to ensure that it is safe to prescribe the medication from a cardiac point of view...



# How do we assess safety and what are we looking for?

- Unidentified structural heart disease (many referral letters are from psychiatry doctors who may not have examined the patients cardiovascular system)
- Pre-existing abnormalities of cardiac conduction
- Any condition with potential for a serious change with ADHD medication





# The scale of the ADHD problem

- Disorder characterised by increased activity, an inability to concentrate, and poor school performance
- 8-10 per cent of all 10-year-old boys in the United States are now diagnosed with ADHD
- 2.5 million children in the US now take stimulants for ADHD
- Adult ADHD is a recent diagnostic phenomenon but 1.5 million adults now diagnosed



# Which Drugs are commonly used?

- [methylphenidate](#) (Ritalin, Methylin, Concerta, Focalin, Metadate), [dextroamphetamine](#) (Dexedrine), and mixed amphetamine salts (eg, Adderall) are effective in improving behaviour in these patients
- Atomoxetine sometimes used in patients with adverse effects to stimulants
- Risperidone is occasionally added



# Pharmacology - Methylphenidate

- Time to initial effect ranges from 20 to 60 minutes
- The duration of action is three to five hours and the half-life is two to three hours.
- Long acting preparations are available and are generally a mixture of immediate and gradual release preparations. Onset 20-60 mins and last up to 12 hours.



# Pharmacology - Amphetamines

- prescribed as a single salt or as mixed dextroamphetamine – amphetamine salts
- Immediate and sustained release preparations, onset 20-60 mins with duration up to 13 hours





# General side effects of stimulant medications

- Relatively common side effects include anorexia, poor growth or weight loss, sleep disturbance, jitteriness, and emotional lability
- Less common side effects include increased heart rate and blood pressure, headache, dizziness, gastrointestinal symptoms, priapism, and peripheral vasculopathy
- Rarely may develop psychotic symptoms (1.48 per 100 person years)
- Long-term Amphetamine use in animal models can induce chronic heart failure



# Known Cardiac Effects of Stimulants

- Studies have found a modest cardiovascular effect at treatment doses
- Pulse increased by 3-10 bpm
- Systolic BP increased by 3-8mmHg
- Diastolic BP by 2-14mmHg
- Assessment performed using extended release methylphenidate in adolescents (mean 14 years)



# Timing of cardiac effects

- Assessed at baseline, 6 weeks, 3 months and 6 months
- HR mean increased from 82-86bpm by 6 weeks. No further changes seen
- Mean SBP increased gradually (113, 115, 115, 117)
- No significant changes in DBP or in ECG findings. No documented arrhythmias



# Other Drugs - Atomoxetine

- alternative to stimulants for children ( $\geq 6$  years)
- oral capsule and can be taken once or twice per day (duration at least 10-12 hours)
- Full therapeutic response not achieved until 6-12 weeks
- metabolized through the cytochrome P450 pathway
- stimulatory effect on the sympathetic nervous system
- Possible increased risk of suicidal thoughts but not actual suicide risk. Rare other psychiatric effects.
- Very rare risk of serious liver disease





# Atomoxetine

- selective norepinephrine/ noradrenaline reuptake inhibitor, which is used as an alternative to stimulant therapy
- Causes clinically important changes in heart rate ( $\geq 20$  beats per minute) or blood pressure ( $\geq 15$  to 20 mmHg) in about 5 to 10 per cent of paediatric patients



# Atomoxetine

- Not therefore recommended in children for who a modest increase in heart rate or blood pressure would be expected to cause problems
- Left up to the individual clinician to decide on prescribing



# Other Drug classes - Alpha-2-adrenergic agonists (clonidine)

- Usually used in children who respond poorly to stimulants or have side-effects
- Can reduce symptoms but not as effective as stimulants
- Side effects include sedation, depression, bradycardia, headache, and possible hypotension
- No evidence of significant tachyarrhythmia or sudden death risk



# Other Drugs - Anti-depressants

- systematic review of four trials comparing tricyclic antidepressants with methylphenidate found either no difference in response or slightly better results with methylphenidate
- mild increases in diastolic blood pressure and pulse rates
- Tri-cyclic antidepressants can cause arrhythmia and are therefore rarely used in children





# Newer anti-depressants

- Selective Serotonin Reuptake Inhibitors do not show an increased risk of adverse cardiac events
- Cause a minor slowing of heart rate and decrease in blood pressure
- Reduction in QTc (but not to significant levels)
- SNRIs also considered cardio-vascularly safe



# Other Drugs - Anti-psychotics

- Drugs such as Risperidone are more frequently being prescribed for adolescents either for psychoses or behavioural problems
- Although the rates of significant cardiac effects are low, the current evidence suggests that there is an overall doubling of the rates of sudden cardiac death in patients treated
- There is no specific data available on the effects in children but caution is advised



What is the evidence for cardiac side-effects?

# **WHY HAVE CARDIOLOGISTS BECOME INVOLVED?**



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# Why has everyone been so worried about the effects of stimulants?

- Individual case reports from the US suggested episodes of sudden death, myocardial infarction and stroke in patients on ADHD stimulants (from Adverse Event Reporting System of the Food and Drugs Agency)
- Overall a total of 25 cases of sudden death (some with post mortem evidence of previously undiagnosed structural disease such as HOCM)
- In Feb 2006 the FDA issued a “black box” warning on all stimulant drugs used to treat ADHD





# Black Box warning

- A **black box warning** is the strictest **warning** put in the labelling of prescription drugs or drug products by the Food and Drug Administration (**FDA**) when there is reasonable evidence of an association of a serious hazard with the drug.



# Current 2016 FDA position

- In an updated safety review, the US Food and Drug Administration (FDA) summarized the findings of the largest cohort study in children that did **not** show an association between ADHD pharmacotherapy and adverse CV events
- Recommend that clinicians prescribe these medications according to the professional prescribing label, and that patients continue to use prescribed therapy for the treatment of ADHD



# The largest study – Cooper et al NEJM 2011

- Retrospective cohort study
- Cases identified from health records
- 4 geographically and culturally distinct health plans
- Total of 1.2 million children and young adults between 2 and 24 years old (mean 11yrs)
- 2.5 million person years of follow up
- 373667 years of ADHD drug use



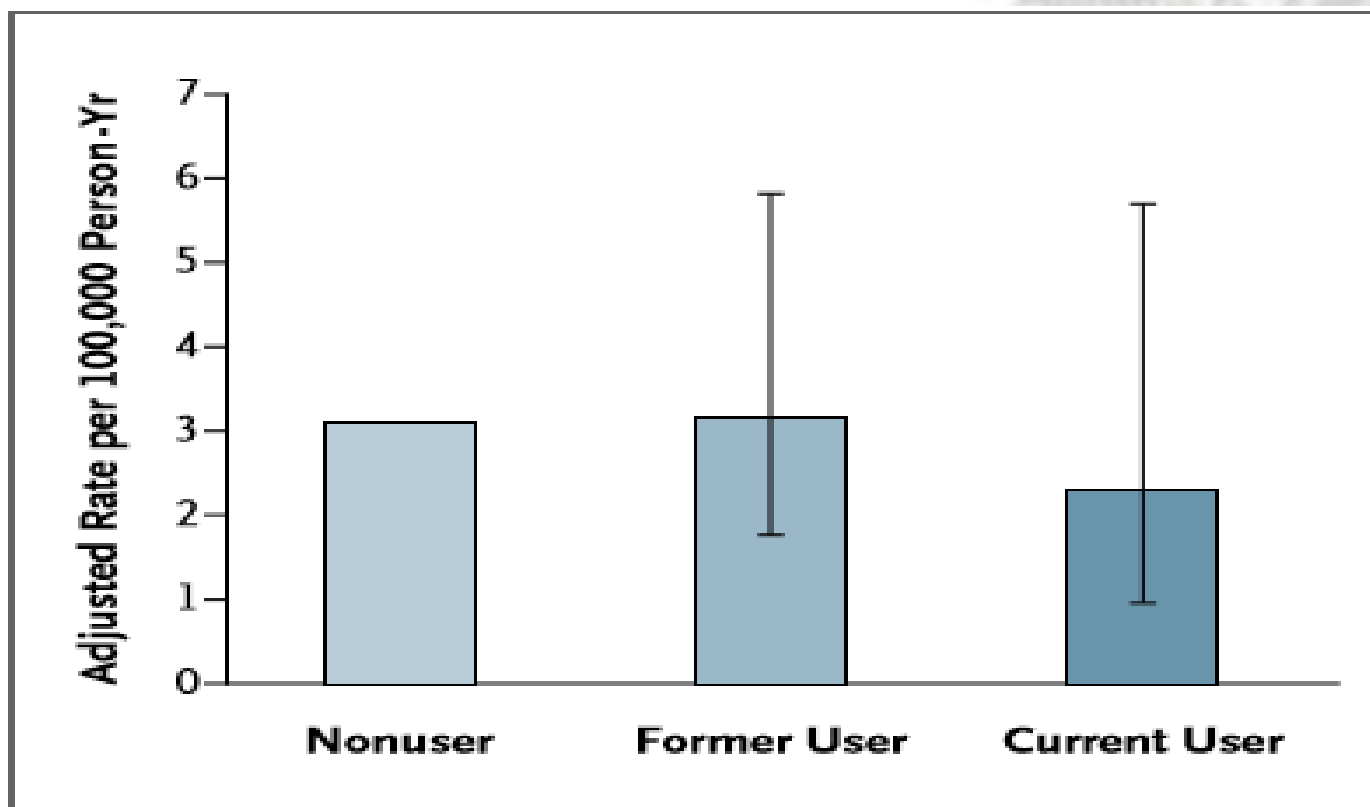
# Results

- Cohort members had 81 serious cardiovascular events (3.1 per 100,000 person years)
- Current users of ADHD meds were not at increased risk (hazard ratio 0.75)
- Risk was not increased for current users compared to previous users (HR 0.70)
- No significant association between use of ADHD drug and sudden death, heart attack or stroke





# Sudden Death Rates



**Figure 1.** Adjusted Rates of Serious Cardiovascular Events, According to the Use of ADHD Drugs.



# Conclusions of the study

- With such a large study, if a significant effect of stimulant ADHD drugs on sudden cardiac death existed it would be expected to have shown
- There is no evidence of a link



# Current International Advice

- Patients should be reviewed by a clinician
- A detailed history including family history of sudden death should be taken
- A cardiovascular examination should occur
- Further evaluation including cardiac studies is neither necessary nor indicated



# FDA Recommended monitoring

- Patients should be monitored for changes in heart rate and blood pressure on an occasional basis
- Stimulant therapy generally should not be prescribed in patients with serious heart problems
- In these individuals, if ADHD therapy is deemed necessary, it should be managed in consultation with a cardiologist





# Children without cardiac disease

- Children without cardiac disease who receive stimulant therapy are **not** at increased risk for Cardio Vascular events compared with the general paediatric population
- stimulant pharmacotherapy can be initiated in a child with ADHD if there is no evidence of cardiac disease based upon a comprehensive CV-focused history and physical examination (current AHA and academy of paediatrics guidelines)



# Children with structural cardiac disease

- ADHD is found in a significant number of children with congenital heart disease
- No evidence that the risk of Sudden Death is higher in patients with CHD when they are treated with stimulant medications
- No data to suggest that specific forms of CHD carry an increased risk of SUD in association with ADHD drugs



# Children with Inherited Cardiac Conditions

- Case-control study of 48 children with LQTS treated with ADHD medications (chiefly stimulants) and followed for approximately eight years, the rate of syncope was greater than that of age-, gender-, and QTc duration-matched patients with LQTS not taking ADHD medications (30 versus 14 percent)
- Other major cardiac events, such as cardiac arrest and LQTS death were rare, and did not differ between groups



# What about adults?

- Among adult patients who are either current or new users of stimulant medications, there appears to be no increased risk of serious CV events. (Risk in the overall cohort was 1.34 per 1000 person-years)
- lower risk of serious CV events (defined as myocardial infarction, stroke, and sudden cardiac death) in individuals who were current users of stimulant therapy versus nonusers (Relative risk 0.83)





# Who are we trying to screen for?

- The question remains as to whether there are any cardiac conditions, including any associations with sudden cardiac death, in which there is a clear-cut contraindication to the use of a stimulant medication
- Current evidence suggests that there is not a contraindication for stimulant medication in patients with ADHD who have no evidence of cardiac disease based upon a comprehensive cardiovascular focused history and physical examination



# The problem with delaying treatment to obtain cardiac review

- no specific cardiac condition for which there is clear-cut evidence that the use of ADHD medications should be contraindicated
- What is clear, however, is limiting or delaying children's access to effective treatment for ADHD could have serious implications in patients who are not effectively treated (increased risk of substance abuse, academic failure and accidents)



# Do all patients need an ECG?

- Routine electrocardiogram (ECG) screening in all patients treated with ADHD stimulant therapy is **not** recommended
- incidence of sudden cardiac death appears to be either lower or similar to that in the general paediatric population
- no data of any ECG findings associated with an increased likelihood of a serious cardiac adverse event due to ADHD therapy



# Outcomes of non-targeted ECG screening

- Retrospective study of 1470 children with ADHD receiving pharmacotherapy that were screened with an ECG from April to September of 2008
- interpreted as abnormal in 119 patients (8.1%)
- echocardiogram, stress test, and Holter monitor identified cardiac disease in five subjects





# Positive results from ECG screening

- 2 Bicuspid aortic valves
- 1 moderate ASD
- 2 asymptomatic delta waves
- None of these would currently be considered a contra-indication to ADHD stimulant therapy



# Overall message

- Stimulant medications, anti-depressants and anti-psychotics are being used increasingly in the paediatric population
- There is concern (particularly among psychiatric doctors) based on previous case reports that these drugs may be dangerous
- There is no evidence to support this suspicion and in fact the largest trial shows a lower rate of sudden death whilst on the medication



# To answer the referrals

- The drugs are generally safe
- These patients do not need cardiology review
- But, before a prescription is given someone should at least listen to their heart



Any Questions?

# THANK YOU



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