

Highlighted Abstract

Members of CADDRA's Advisory Council will select a monthly abstract based on its clinical relevance. The commentary reflects the reviewer's own opinion and is not approved, or necessarily representative, of the opinion of the CADDRA board. This month's abstract was selected by one of our newest board members, **Dr. Russell J. Schachar**.

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Attention-Deficit/Hyperactivity Disorder Medications and Long-Term Risk of Cardiovascular Diseases

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Zhang and colleagues examined the impact of ADHD medication use on cardiovascular health in a large sample of individuals with a diagnosis of ADHD. This study was conducted using data from Sweden where prescriptions and health diagnoses are recorded in centralized and accessible data bases. Researchers first identified individuals aged 6 to 64 years with an ADHD diagnosis or treatment with an ADHD medication (methylphenidate, dextroamphetamine, lisdextroamphetamine, or atomoxetine) between January 1, 2007, and December 31, 2020. Using their access to patient health records, they looked to see which of these individuals developed cardiovascular disease (CVD) later in life. Using publicly available data, they "followed" these individuals until December 31, 2020 (some people were followed for 13 years whereas others were followed for only a few months).

CVD was defined as arrhythmias, arterial disease, cerebrovascular disease, heart failure, hypertension, ischemic heart disease, or thromboembolic disease. The researchers excluded anyone who had one of these cardiovascular diseases before

baseline, individuals whose medication prescriptions was for a condition other than ADHD and individuals who emigrated or died during the follow-up period.

The median length of follow up was 4.1 years. Two thirds of the study sample were older than 25 with a mean age of 42 years. One third of the study sample were younger than 25 years with a mean age of 15.8 years. There were 10388 ADHD individuals with CVD (ADHD+CVD). They matched these participants to 51672 individuals without CVD (ADHD-CVD). They were interested in the difference between these two groups in exposure to ADHD medication.

What were the key findings of this study?

- Risk for developing CVD was associated with ADHD medication use (23% increased risk for >5 years of ADHD medication use compared with non-use).
- Increased risk was noted for hypertension and arterial disease but not for arrhythmias, heart failure, ischemic heart disease, thromboembolic disease, or cerebrovascular disease.
- It was duration of exposure and dose that caused greatest risk, not whether or not participants were exposed to ADHD medication. In fact, both groups had the same exposure to stimulants: 83.9% of ADHD cases with CVD and 83.5% of ADHD cases who did not develop CVD used ADHD medication during follow-up.
- What mattered was duration of drug use. Longer cumulative duration of ADHD medication use was associated with increased risk of CVD compared to non-use. Risk for CVD increased from no effect for treatment lasting less than one year to a 23% increase in risk for treatment lasting longer than 5 years.
- It appeared that risk increased greatest in first 3 years and then became stable.
- Risk increased with higher average daily dosages (> 60 mg MPH had greater impact than 45 to ≤60).
- Increased risk stabilized after the first several years of medication use and persisted throughout the 4-year follow-up period.
- Risk was similar in males and females, children, and adults.
- Similar increase in risk for CVD found with methylphenidate, dextroamphetamine, lisdextroamphetamine. The effect of atomoxetine was seen only for the first year of use.

- Study did not find any association between ADHD medication use and the risk of arrhythmias which can be the cause of “sudden cardiac death”.
- Methylphenidate was most common drug used followed by atomoxetine and lisdexamfetamine.

What did the study’s authors conclude?

- Long-term exposure to ADHD medications was associated with an increased risk of CVDs, especially hypertension and arterial disease.
- It is important to carefully weighing potential benefits and risks when making treatment decisions about long-term ADHD medication use.
- Clinicians should regularly and consistently monitor cardiovascular signs and symptoms throughout the course of treatment.
- This is an important study which finds a statically significant association of cardiovascular disease, especially hypertension and arterial disease, ADHD and ADHD medication.
- Note that individuals with pre-existing cardiovascular conditions were excluded from this study so the study does not pertain to treatment of individuals with known CVD.
- The magnitude of the reported relationship between duration and dose of ADHD medications and CVD that is found in the Zhang et al study is small and by many standards trivial and does not, by itself, justify the recommendation that clinicians should regularly and consistently monitor cardiovascular signs and symptoms throughout the course of treatment.
- According to existing guidelines, initial assessment should involve a biopsychosocial assessment including questioning about CVD and regular monitoring of heart rate and blood pressure (see Canadian ADHD Practice Guidelines, 4.1 Edition, CADDRA 2020).
- The study draws attention to the relationship of ADHD and cardiovascular disease risks (higher body mass index, systolic and diastolic blood pressure, triglyceride levels and being a current smoker) (Thapar et al., 2023). The researchers had to exclude 2.5% of ADHD participants because of the presence of cardiovascular disease at baseline even though cardiovascular disease is found in 0.7% of this general population. That is a substantial elevation of risk for cardiovascular disease in ADHD whether treated with medication or not. Genetic studies have shown a relationship between

genetic risk for ADHD and risk for cardiovascular disease (weight, obesity, smoking and longevity) (Demontis et al., 2017; Garcia-Argibay et al., 2022).

- The study sheds some light on an important unresolved question about ADHD: Why do individuals with a diagnosis of ADHD seem to have a shorter life expectancy? Cardiovascular disease caused by ADHD medications might play a role in shortening life expectancy.

Does this study affect clinical practice?

- There are good reasons for using ADHD drugs in the treatment of ADHD. Systematic reviews and meta-analyses provide convincing evidence about the short-and-long term benefits of medication on ADHD symptoms, impairments, and learning and the magnitude of these effects exceeds that seen with other interventions.
- The call to monitor cardiovascular signs and symptoms throughout the course of treatment should consider the risks of monitoring such as financial cost and the likelihood of incidental findings or the benefits such as how many lives would be saved if such monitoring took place. These important questions need further study.
- Specific guidelines for what should be monitored and how (frequency, type of monitoring) are needed, as are directives about what happens when atypical results are obtained. The Zhang et al study does not specify the nature of cardiovascular monitoring.
- The recommendation made by the authors that it is important to weigh potential benefits and risks when making treatment decisions about long-term ADHD medication use is sensible and appears in current practice guidelines for ADHD and other conditions.
- Clinical practice guidelines (e.g., Canadian ADHD Practice Guidelines, Edition 4.1, CADDRA 2020) recommend a comprehensive assessment involving physical, mental and social wellbeing before reaching a diagnosis of ADHD in children or adults and prior to starting treatment of any kind. And current guidelines recommend monitoring of patients who are taking medication including monitoring of physical, mental and social wellbeing. There is no reason to change clinical practice based on the results of the current study.

References

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