Cardiovascular Considerations for Stimulant Class Medications

Paul Hammerness, MD[a,*], Amy Berger, BS[b], Michael C. Angelini, MA, PharmD[c], Timothy E. Wilens, MD[b]

KEYWORDS

• Cardiovascular • Stimulant • ADHD • Blood pressure • Heart rate • ECG

KEY POINTS

- Stimulant-related minor increases in blood pressure (BP) and heart rate (HR) have been well described, albeit principally reported as group-level data, in short-term treatment of healthy samples.
- Subjective complaints of a cardiovascular (CV) or cardiopulmonary nature tend to be isolated experiences and have not been associated with serious CV outcomes, noting the very low absolute risk of serious outcomes challenges detection in epidemiologic investigations.
- Recommendations regarding stimulant treatment in the presence of medical comorbidities are beginning to emerge, with future investigations needed to support sophisticated identification of risk based on structural or dynamic pathophysiology.
- Attention to stimulant-associated CV risk is an opportunity for clinicians treating pediatric attention-deficit hyperactivity disorder (ADHD) to engage in general CV risk identification and intervention, such as targeting physical inactivity, Tobacco use, and childhood obesity.

BACKGROUND

First-line treatment for attention-deficit hyperactivity disorder (ADHD) includes methylphenidate (MPH) and amphetamine (AMP)-based stimulant medications. The cardiovascular (CV) impact of stimulants has been considered for decades given inherent sympathomimetic effects.[1] CV findings on stimulants have been typically presented as clinically nonsignificant increases in resting blood pressure (BP) and heart rate (HR) in the context of short-term clinical trials, with healthy prescreened participants. Following a series of serious CV events in the setting of stimulant medications, large-scale epidemiologic studies were conducted in pediatric and adult populations. While the association between stimulants and serious CV events has not determined

[a] Psychiatry Services, Southcoast Health, 101 Page Street, New Bedford, MA, USA; [b] Child and Adolescent Psychiatry, Massachusetts General Hospital, 55 Fruit Street, Boston, MA, USA; [c] Massachusetts College of Pharmacy and Health Sciences University, Boston, MA, USA
* Corresponding author.
E-mail address: hammernessp@southcoast.org

Child Adolesc Psychiatric Clin N Am 31 (2022) 437–448
https://doi.org/10.1016/j.chc.2022.02.002 **childpsych.theclinics.com**

causality, there is no unifying mechanism to understand stimulants' impact on the CV system beyond known sympathomimetic activity. In addition, there is no understanding of mediating variables and moderating processes in the relationship between stimulants and CV outcomes, with particular uncertainty in regards to the medically complex/vulnerable patient. In this article, we will review the underlying literature on this subject as well as make clinical recommendations on screening to mitigate potentially adverse outcomes.

CURRENT EVIDENCE

Mean elevations in HR and BP on stimulants have been reported for decades. A series of studies were conducted in the 1970s–1980s, using small samples but with a targeted methodology. Readings were taken typically 1 to 2-hours postdose, principally after immediate-release MPH administration. Significant increases in HR versus placebo were described, including greater elevations in medication-naïve subjects as well as dose dependency.[2–5] With the arrival of extended duration formulations, HR and BP outcomes were reported in the context of large, placebo-controlled studies, with measurements typically ~ 8 to 10-hours postdose. Significant increases in HR ($\leq$9 bpm) versus placebo ($\leq$1bpm) were documented across extended-release MPH and AMP agents.[6–9]

Subsequent open extension clinical trials (6–24 months) showed persistent elevations in HR (1–5 bpm) and BP (1–5 mm Hg), consistent with a lack of tolerance to stimulants' effects on HR, and with an apparent absence of dose-dependency. Longer term, 2 to 14 year ADHD cohorts, offered nonconclusive findings given small numbers of consistent medication users, and uncertain actual exposure.[7,8,10–16] Recent naturalistic reports find unchanged BP, with significant elevations in HR,[17] and conversely, declining BP over 12 years of stimulant without significant HR change.[18] Limitations that remain in the interpretation of naturalistic reports include the nonverified medication intake and details around the collection of BP/HR.

In addition to mean HR and BP changes, some clinical reports include frequency of vital sign outliers, who are defined as exceeding a threshold (eg, $\geq$120/80 mm Hg) or per change from baseline (eg, increase in SBP$\geq$20 mm Hg, HR > 25bpm), at least once on medication. Outlier rates are typically 5% to 15% in shorter and longer term treatment. When reported, outlier elevations seem sporadic, with less than 5% occurring at consecutive visits.[7,8,19–23] The clinical relevance or intervention for these outliers remains unknown.

There have been few investigations of moderators of BP/HR outcomes during therapeutic stimulant treatment. The US FDA Center for Drug Evaluation and Research conducted a novel study of stimulant formulation in healthy adults. BP and HR changes were found to be highly dependent on MPH pharmacokinetics.[24] However, in an extensive review of pediatric clinical trials (N = 5837), Hennissen (2017) found no effect of medication type or dose, along with age, gender, or comorbidity.[25]

In addition to objective BP and HR findings, subjective experiences of a possible CV or cardiopulmonary nature have been well documented in the clinical trial literature. Palpitations, tachycardia, chest pain/tightness, and dyspnea are most common, in up to ~20% of stimulant-treated subjects and can occur more frequently than on placebo. In a rare investigation of moderating/mediating variables, Hammerness[22] found elevated rates of comorbid anxiety disorders in those adolescents with consecutive CV complaints, albeit not a primary outcome with sufficient power to offer conclusions. Emergency room, naturalistic presentations document similar subjective complaints in stimulant-treated patients, yet serious events associated with complaints are

rare and consistent with rates of persons not receiving stimulant medications.[12,19,23,26–29]

SERIOUS OR RARE CARDIOVASCULAR EVENTS

In the 1990s and early 2000s, serious CV events in youth prescribed stimulants raised clinical, scientific, and public health questions about the safety of ADHD treatment. The 1990s cases of sudden death involving children receiving clonidine alongside MPH[30] were not attributed to either medication or to their combination. Investigations of concomitant MPH and clonidine as well as tricyclic antidepressants subsequently shifted focus to serious CV adverse outcomes (eg, heart attack, death) associated with stimulants alone.[31] Multiple epidemiologic, registry and case control studies have been undertaken since then, with the preponderance of evidence finding no causal relationship between therapeutic stimulants and serious, life-threatening CV outcomes (ie, sudden death, myocardial infarction, and stroke). Actual rates are low, highlighting the challenge of such investigations.[32–38] When observed, rates of serious CV events on stimulants including sudden cardiac death are not different from known general population rates (1.32 per 100,000 persons in children and young adults).[39] Methodological issues limit the interpretation of positive findings,[31] yet confidence intervals for pooled estimates do not exclude a modest increase in risk.[40,41]

Taking the sum of the literature, US FDA concluded the rate of sudden death with stimulants was less than national rates and the Pediatric Advisory Committee deemed a black box warning was not indicated. Instead, FDA issued warnings about stimulants in underlying CV disease and directed the creation and implementation of Medication Guides. However, a recent evaluation of professional and consumer labels for ADHD medications registered in Australia, Canada, UK, and US finds inconsistencies in the description of stimulants' CV risk profile.[42]

Responsive to what seems to be another rare event, albeit of lower severity, a major change to US warnings occurred in 2013; "Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment."[43] Limited case report references exist in the pediatric (therapeutic) literature to support this association. For example, Yu et al (2010) described 4 boys with ADHD who developed vasculopathy following mean 6 years of stimulant exposure.[44] A recent case series (N = 16) of adults receiving treatment with AMP stimulants described generally mild vasospastic symptoms of the extremities.[45] Severe vascular manifestations were associated with a history of rheumatologic disease, found in 25% of the sample. However, is possible that peripheral vasculopathy occurs more often the literature suggests, as this adverse event is not systematically assessed for in clinical studies.

GUIDELINES AND RECOMMENDATIONS

Recommendations from American Academies of Pediatrics, Child and Adolescent Psychiatry, and American Heart Association recommend a CV focused patient and family history and physical examination for youth before the initiation of stimulant medication for ADHD.[37,46–48] The aim is to identify patients with undiagnosed underlying CV disease, for example, structural disorders (**Table 1**).

Potential cardiac origin symptoms include fainting or dizziness (exertional, emotional), chest pain (central, crushing, exertional), worsening exercise tolerance, palpitations, increased HR, extra/skipped beats, and seizures (exertional, emotional). Family member's relevant history includes sudden or unexplained death in young (<40 years), sudden death during exercise, cardiac arrhythmias, cardiomyopathy,

Table 1
Recommendations for cardiovascular screening when using stimulant medications for ADHD

Medical History (screening for sudden death risk)	• Personal congenital or acquired cardiac disease • Palpitations, chest pain, syncope, unexplained dizziness, fainting, shortness of breath or seizure, postexercise symptoms • Family history of premature cardiac disease (< 30 years of age), history of sudden or unexplained death including drowning or motor vehicle accident • Other medications including over the counter that affect the heart • Routine medical and family cardiac istory
Vital Signs; Routine Care	• Blood pressure/heart rate at baseline and periodically thereafter • No ECG, Holter, or exercise testing necessary in routine care
Suspicion of CV disease (eg, hypertrophic cardiomyopathy; ion channelopathies)	• Consult pediatric (or adult) specialty care, for example, cardiology, with workup as indicated by clinical history and symptoms

Recommendations derived from the American Heart Association and American Academy of Pediatrics.[32,46,63–66]

and presence of connective tissues diseases (eg, Marfan syndrome.) Any concerns before during treatment should be shared with primary care and/or specialists for the consideration of further evaluation.

Following the initiation of a stimulant, recommendations are generally to *periodically* monitor for changes in HR or BP in healthy children, with assessments recommended to occur *at every health encounter* for those at theoretic increased risk, such as in presence of complex medical conditions or concomitant medications known to increase BP.[49–55] If elevated BP is observed per appropriate protocol,[55] repeat measurements are indicated with primary/specialty care consultation, including the consideration of ambulatory BP monitoring.[56] Canadian ADHD Resource Alliance (CADDRA) Guidelines for individuals across the lifespan recommend initial BP assessment before starting medication, and then during follow-up, with closer monitoring for those with HTN or coronary heart disease. While not recommending a frequency of follow-up assessment, CADDRA recommends taking measurements while the medication is present in the system, as it may be useful to compare to findings before a dose is taken.[57]

In addition to BP monitoring, CV review during treatment can identify concerning complaints (crushing, exertional chest pain, extra/skipped beats). When present, symptoms should be communicated for shared decision making.[46,47,56,58] Thoughtful documentation of normative/baseline CV experiences before stimulant initiation, such as racing heart during exertion or with anxiety, will aid in a possible later review.

For those who do not tolerate an initial stimulant trial, such as mild subjective discomfort, without a determined contraindication to continue pharmacotherapy (eg, new/unstable CV finding), an alternate form of stimulant may be considered. Theoretically, differences in pharmacokinetics among stimulants may impact CV tolerability although this has been understudied.[24] A nonstimulant may be considered as well, given these agents offer differing CV impacts based on pharmacodynamics. While noradrenergic atomoxetine and viloxazine also result in elevations in BP/HR,[25,59,60] the converse risk (ie, hypotension, bradycardia and syncope) can occur

with monotherapy or adjunctive therapy with the nonstimulant alpha-2-adrenergic agonists' clonidine and guanfacine.[61,62]

CONTROVERSIES

Although screening ECG is not recommended for healthy children/adolescents with ADHD,[37,46,56,67] previous conflicting recommendations from the American Heart Association and American Academy of Pediatrics left clinicians and families uncertain.[46,47] A follow-up joint statement clarified that ECGs were not universally mandatory,[64] yet the practice of screening ECG remained.[65]

Since early examinations, no statistically significant, clinically meaningful changes have been reported in ECG intervals in pediatric samples. A range of subjects (1%–19%) have "abnormal" ECG reports (eg, ST–T wave changes; bundle branch block) consistent with ECG variants found in similar rates in healthy individuals.[7,19,21,23,68–70] QTc prolongation during stimulant treatment when present has been modest,[71] while poor metabolizers of the nonstimulant atomoxetine have demonstrated increased QTC intervals.[69] There is no evidence that any ECG finding is associated with an increased likelihood of serious event due to stimulant medication.[37]

A retrospective study of 1470 children on ADHD medication with "abnormal" ECG in screening led to the identification of true abnormality in 0.3% of sample, at a cost to identify each case of $17,000.[72] Instead, referral is recommended if clinical CV concern (eg, palpitations, syncopal episodes) before initiation or during the course of treatment.[1,37,46,56,67]

COMPLICATIONS/CONCERNS

Concerns expressed include the uncertain impact of cumulative stimulant exposure, as well as the devolving baseline physical health of the pediatric population. At present, ADHD patients are typically prescribed an extended duration form of stimulant, year-round, with potential exposure for decades. It is not known if greater exposure over the course of the day or cumulatively over years impacts the distribution of risk.

In addition, the physical health profile of US children is concerning, with the accumulation of CV risk factors that may impact tolerability/safety of stimulant medications. While the onset of tobacco use in adolescence has a potential lifelong impact, the present-day regular/excess use of energy drinks (~30% of adolescents) especially before or during sports, may trigger palpitations and arrhythmias,[73,74] with increases of ~3 to 4 mm Hg BP documented across 15 adult studies.[75] Elevated BMI (~50% of teenagers), is particularly startling given that rates of hypertension increase with increasing adiposity; from 4% to 25%.[55] CV disease risk accumulates the earlier children develop their obesity, with detectable precursors of atherosclerosis by the time a child enters middle school.[75] All participants in health care delivery should be engaged in recognizing and monitoring individuals who are overweight or obese.[76]

In sum, data collected in past years regarding CV impact may not similarly inform risk: benefit considerations for today's patient. It is important to note these concerns reflect theoretic risk and offer areas of future investigation as well as public health engagement.

MEDICAL COMORBIDITIES

While there is no specific form of heart disease identified to be of greatest concern,[37] stimulants' CV risk may be mediated by a given patient's vulnerability. Few clinical investigations have examined specific CV populations such as a small sample of adults

with ADHD and hypertension.[77–79] In a nationwide insurance database in South Korea, highest risk of arrhythmia was seen in children with Congenital Heart Disease; despite an increased relative risk, the absolute risk was low.[77] In a small sample of children (N = 28) with known long QT-syndrome, none of the children on stimulant experienced QT-related events.[80]

The Spanish Society of Pediatric Cardiology and Congenital Heart Disease recently outlined a comprehensive and individualized approach with considerations per specific cardiac condition. For example, the society recommends individualized pharmacologic treatment in those sensitive to potential tachycardia, such as in the setting of diastolic dysfunction or mitral stenosis in whom a shortening of the diastole should be avoided, or patients with systolic dysfunction in whom an increase in myocardial oxygen consumption secondary to tachycardia should be avoided.[56] Medications were not advised for a limited number of high-risk patients, including hemodynamically unstable CHD, residual hypertension, catecholaminergic polymorphic ventricular tachycardia, and frequent/complex PVCs.[56,81]

FUTURE DIRECTIONS

Critical questions remain about the mechanisms of stimulant's CV impact.[82] Abnormal sympathetic tone,[83] physiologic adaptations,[1,77] direct pathologic changes[84,85]; or peripheral vascular changes[86] are possible etiologic pathways. Finally, cardiopulmonary symptoms (eg, dyspnea) may indicate exercise-induced pulmonary arterial hypertension, diastolic dysfunction or peripheral muscle dysfunction.

Studies using dynamic assessments[77,87] and advances in methodology may be used to investigate a range of possible mechanisms. Risk may be determined to vary, according to a range of mediators (eg, age, gender, family CV history) and moderators (eg, tobacco use, stimulant dose, duration, formulation).

On the contrary, stimulant treatment of ADHD may be cardio-protective, with associated, albeit indirect, improvements in functioning and reductions in emotional reactivity.[58] As per Skinner's commentary regarding patients with long QT syndrome,[88] therapeutic stimulants may be associated with the removal of peaks in HR due to improved temper and behavioral control. In addition, stimulant treatment may lead to further indirect cardio-protection via improvements in physical health, and attention to self-care (eg, adherence to eating, sleeping, exercise regimens).[89,90]

SUMMARY

Stimulant-class medications for healthy children and adolescents with ADHD continue to be associated with mean elevations in BP ($\leq$5 mm Hg) and HR ($\leq$10 beats/min) without changes in electrocardiographic parameters. A subset (5%–15%) of children and adolescents may have a greater increase in HR or BP or may report a CV-type complaint during treatment. Serious CV events during stimulant treatment are rare and similar to groups of children not receiving stimulant medication. Despite the stability of these findings, CV may be considered dynamic, related to underlying (medical) vulnerability in a given patient, in response to alterations in prescribing, or impacted by the baseline health of the treated population. Screening includes CV-focused history before stimulant initiation, as well as monitoring of HR/BP and for novel subjective complaints in the context of treatment. Lifespan guidelines do not distinguish specific risk nor offer recommendations per age, besides that related to monitoring in the presence of increased medical comorbidities.[58]

CLINICS CARE POINTS

- Expect minor increases in HR, BP on stimulant, with outliers having greater change
- Subjective reports of a seemingly CV nature occur infrequently, without evident-associated serious CV outcomes
- Rare serious CV events occur without evident causality
- CV screening of all patients being considered for, and occurring while taking stimulant medication may identify those with underlying structural or other cardiac abnormalities—positive findings should result in collaborative care with primary and speciality care
- There remains insufficient evidence to guide risk assessment for a given patient, particularly for medically complex, although guidelines are emerging
- Opportunities exist to support public health monitoring of general CV risk factors, namely elevated BMI and BP, although stimulant attributable CV risk for such vulnerable patients is theoretic

DISCLOSURE

Dr P. Hammerness receives royalties from the following publications: *ADHD, Biographies of a Disease*, Greenwood Press, 2009; *Organize Your Mind, Organize Your Life*, Harlequin Press/Harvard University, 2012; *Straight Talk about Psychiatric Medications for Kids*, Guilford Press 2016. Dr P. Hammerness also receives royalties from Massachusetts General Hospital, owner of a copyrighted questionnaire co-developed with Dr T. E. Wilens, licensed to Ironshore Pharmaceuticals (*The Before School Functioning Questionnaire*). A. Berger has nothing to disclose. Dr M.C. Angelini has received speakers' honoraria from Alkermes, Inc. Dr T. E. Wilens is Chief, Division of Child and Adolescent Psychiatry and (Co) Director of the Center for Addiction Medicine at Massachusetts General Hospital. He receives grant support from the following sources: NIH (NIDA). Dr T. E. Wilens has published a book, Straight Talk About Psychiatric Medications for Kids (Guilford Press), and co/edited books: ADHD in Adults and Children (Cambridge University Press). Dr T. E. Wilens is co/owner of a copyrighted diagnostic questionnaire (Before School Functioning Questionnaire) and has a licensing agreement with Ironshore (BSFQ Questionnaire). He is or has been a consultant for Arbor Pharmaceuticals, 3D Therapeutics, Vallon, and Ironshore, and serves as a clinical consultant to the US National Football League (ERM Associates), US Minor/Major League Baseball; Gavin Foundation and Bay Cove Human Services.

REFERENCES

1. Hammerness PG, Perrin JM, Shelley-Abrahamson R, et al. Cardiovascular risk of stimulant treatment in pediatric attention-deficit/hyperactivity disorder: update and clinical recommendations. J Am Acad Child Adolesc Psychiatry 2011; 50(10):978–90.
2. Solanto MV, Conners CK. A dose-response and time-action analysis of autonomic and behavioral effects of methylphenidate in ADHD. Psychophysiology 1982; 19(6):658–67.
3. Kelly KL, Rapport MD, DuPaul GJ. Attention deficit disorder and methylphenidate: a multi-step analysis of dose-response effects on children's cardiovascular functioning. Int Clin Psychopharmacol 1988;3(2):167–81.

4. Tannock R, Schachar RJ, Carr RP, et al. Dose-response effects of methylphenidate on academic performance and overt behavior in hyperactive children. Pediatrics 1989;84(4):648–57.
5. Safer DJ. Relative cardiovascular safety of psychostimulants used to treat ADHD. J Child Adolesc Psychopharmacol 1992;2(4):279–90.
6. Rapport MD, Moffitt C. ADHD and methylphenidate. A review of height/weight, cardiovascular, and somatic complaint side effects. Clin Psychol Rev 2002; 22(8):1107–31.
7. Wilens TE, Spencer TJ, Biederman J. Short- and long-term cardiovascular effects of mixed amphetamine salts extended-release in adolescents with ADHD. CNS Spectrums 2005;10(S15):22–30.
8. Findling RL, Biederman J, Wilens TE, et al. Short- and long-term cardiovascular effects of mixed amphetamine salts extended release in children. J Pediatr 2005;147(3):348–54.
9. Weisler R, Adler L, Hamdani M et al. Cardiovascular outcomes in children and adults treated with lisdexamfetamine dimesylate for ADHD. Paper presented at: Annual Meeting of the American Academy of Child and Adolescent Psychiatry; Honolulu (HI); October 27-November 1, 2009.
10. McGough JJ, Biederman J, Wigal SB, et al. Long-term tolerability and effectiveness of once-daily mixed amphetamine salts (Adderall XR) in children with ADHD. J Am Acad Child Adolesc Psychiatry 2005;44(6):530–8.
11. Findling RL, Childress AC, Krishnan S, et al. Long-term effectiveness and safety of lisdexamfetamine dimesylate in school-aged children with ADHD. CNS Spectr 2008;13(7):614–20.
12. Findling RL, Wigal SB, Bukstein OG, et al. Long-term tolerability of the methylphenidate transdermal system in pediatric ADHD. Clin Ther 2009;31(8):1844–55.
13. Weisler R, Young J, Mattingly G, et al. Long-term safety and effectiveness of lisdexamfetamine dimesylate. CNS Spectr 2009;14(10):573–85.
14. Vitiello B, Elliott GR, Swanson JM, et al. Blood pressure and heart rate over 10 years in the multimodal treatment study of children with ADHD. Am J Psychiatry 2011;169(2):167–77.
15. Arcieri R, Germinario EA, Bonati M, et al. Cardiovascular measures in children and adolescents with ADHD who are new users of methylphenidate and atomoxetine. J Child Adolesc Psychopharmacol 2012;22(6):423–31.
16. Smith G. Raine ADHD study: long-term outcomes associated with stimulant medication in the treatment of ADHD in children. Perth (Western Australia): Government of Western Australia, Department of Health; 2010. Available at: http://www.health.wa.gov.au/publications/documents/MICADHD_Raine_ADHD_Study_report_022010.pdf. Accessed September 27, 2021.
17. St Amour MD, O'Leary DD, Cairney J, et al. What is the effect of ADHD stimulant medication on heart rate and blood pressure in a community sample of children? Can J Public Health 2018;109(3):395–400.
18. Conzelmann A, Müller S, Jans T, et al. Long-term cardiovascular safety of psychostimulants in children with ADHD. Int J Psychiatry Clin Pract 2019;23(2): 157–9.
19. Donner R, Michaels MA, Ambrosini PJ. Cardiovascular effects of mixed amphetamine salts extended release in the treatment of school-aged children with ADHD. Biol Psychiatry 2007;61(5):706–12.
20. Medori R, Ramos-Quiroga JA, Casas M, et al. A randomized, placebo-controlled trial of three fixed dosages of prolonged-release OROS methylphenidate in adults with ADHD. Biol Psychiatry 2008;63(10):981–9.

21. Childress AC, Spencer T, Lopez F, et al. Efficacy and safety of dexmethylphenidate extended-release capsules administered once daily to children with ADHD. J Child Adolesc Psychopharmacol 2009;19(4):351–61.
22. Hammerness P, Wilens T, Mick E, et al. Cardiovascular effects of longer-term, high-dose OROS methylphenidate in adolescents with ADHD. J Pediatr 2009; 155(1):84–9.e1.
23. Findling RL, Katic A, Rubin R, et al. A 6-month, open-label, extension study of the tolerability and effectiveness of the methylphenidate transdermal system in adolescents diagnosed with ADHD. J Child Adolesc Psychopharmacol 2010;20(5): 365–75.
24. Li L, Wang Y, Uppoor RS, et al. Exposure-response analyses of blood pressure and heart rate changes for methylphenidate in healthy adults. J Pharmacokinet Pharmacodyn 2017;44(3):245–62.
25. Hennissen L, Bakker MJ, Banaschewski T, et al. Cardiovascular effects of stimulant and non-stimulant medication for children and adolescents with ADHD. CNS Drugs 2017;31(3):199–215.
26. Cohen AL, Jhung MA, Budnitz DS. Stimulant medications and ADHD. N Engl J Med 2006;354(21):2294–5.
27. Winterstein AG, Gerhard T, Shuster J, et al. Cardiac safety of central nervous system stimulants in children and adolescents with ADHD. Pediatrics 2007;120(6): e1494–501.
28. Winterstein AG, Gerhard T, Shuster J, et al. Cardiac safety of methylphenidate versus amphetamine salts in the treatment of ADHD. Pediatrics 2009;124(1): e75–80.
29. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. (January 24, 2013). The DAWN Report: Emergency Department Visits Involving Attention Deficit/Hyperactivity Disorder Stimulant Medications. Rockville (MD).
30. Popper CW, Zimnitzky B. Child and adolescent psychopharmacology update: J Child Adolesc Psychopharmacol 1996;6(2):85–118.
31. Gould MS, Walsh BT, Munfakh JL, et al. Sudden death and use of stimulant medications in youths. Am J Psychiatry 2009;166(9):992–1001.
32. Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. N Engl J Med 2011;365(20):1896–904.
33. Schelleman H, Bilker WB, Strom BL, et al. Cardiovascular events and death in children exposed and unexposed to ADHD agents. Pediatrics 2011;127(6): 1102–10.
34. Winterstein AG, Gerhard T, Kubilis P, et al. Cardiovascular safety of central nervous system stimulants in children and adolescents: population based cohort study. BMJ 2012;345:e4627.
35. Westover AN, Halm EA. Do prescription stimulants increase the risk of adverse cardiovascular events? BMC Cardiovasc Disord 2012;12:41.
36. Winterstein AG. Cardiovascular safety of stimulants in children. Curr Psychiatry Rep 2013;15(8):379.
37. Berger S. ADHD medications in children with heart disease. Curr Opin Pediatr 2016;28(5):607–12.
38. Zito JM, Burcu M. Stimulants and pediatric cardiovascular risk. J Child Adolesc Psychopharmacol 2017;27(6):538–45.
39. El-Assaad I, Al-Kindi SG, Aziz PF. Trends of out-of-hospital sudden cardiac death among children and young adults. Pediatrics 2017;140(6):e20171438.

40. Liu H, Feng W, Zhang D. Association of ADHD medications with the risk of cardiovascular diseases. Eur Child Adolesc Psychiatry 2019;28(10):1283–93.
41. Cortese S. Pharmacologic treatment of attention deficit-hyperactivity disorder. N Engl J Med 2020;383(11):1050–6.
42. Sieluk J, Palasik B, dosReis S, et al. ADHD medications and cardiovascular adverse events in children and adolescents. Pharmacoepidemiol Drug Saf 2017;26(3):274–84.
43. Label. 2013. Available at: www.fda.gov; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021278s029lbl.pdf.
44. Yu ZJ, Parker-Kotler C, Tran K, et al. Peripheral vasculopathy associated with psychostimulant treatment in children with ADHD. Curr Psychiatry Rep 2010; 12(2):111–5. Accessed September 28, 2021.
45. Tan G, Mintz AJ, Mintz B, et al. Peripheral vascular manifestation in patients receiving an amphetamine analog: a case series. Vasc Med 2019;24(1):50–5.
46. Perrin JM, Friedman RA, Knilans TK. Black Box Working Group; Section on Cardiology and Cardiac Surgery. Cardiovascular monitoring and stimulant drugs for attention-deficit/hyperactivity disorder. Pediatrics 2008;122(2):451–3.
47. Vetter VL, Elia J, Erickson C, et al. Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder [corrected]. Circulation 2008;117(18):2407–23 [Erratum appears in Circulation. 2009;120(7):e55-9].
48. Gutgesell HP. Screening for cardiovascular disease in the young. Congenit Heart Dis 2011;6(2):88–97.
49. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. Pediatrics 2004;114(2 Suppl 4th Report): 555–76.
50. Park MK, Menard SW, Schoolfield J. Oscillometric blood pressure standards for children. Pediatr Cardiol 2005;26(5):601–7.
51. Fox K, Borer JS, Camm AJ, et al. Resting heart rate in cardiovascular disease. J Am Coll Cardiol 2007;50(9):823–30.
52. Pliszka S, AACAP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with ADHD. J Am Acad Child Adolesc Psychiatry 2007;46(7):894–921.
53. Jouven X, Empana JP, Escolano S, et al. Relation of heart rate at rest and long-term (>20 years) death rate in initially healthy middle-aged men. Am J Cardiol 2009;103(2):279–83.
54. Cooney MT, Vartiainen E, Laatikainen T, et al. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. Am Heart J 2010;159(4):612–9.e3 [Erratum appears in Am Heart J 2010;160(1):208. Laakitainen, Tinna [corrected to Laatikainen, Tiina]].
55. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 2017;140(3):e20171904 [Erratum appears in Pediatrics 2017; Erratum appears in Pediatrics 2018;142(3)].
56. Pérez-Lescure Picarzo J, Centeno Malfaz F, Collell Hernández R, et al. [Recommendations of the Spanish Society of Paediatric Cardiology and Congenital Heart Disease as regards the use of drugs in attention deficit hyperactivity disorder in children and adolescents with a known heart disease, as well as in the general paediatric population: position statement by the Spanish Paediatric Association]. An Pediatr (Engl Ed) 2020;92(2):109.e1–7.

57. Canadian attention deficit hyperactivity disorder resource alliance (CADDRA): Canadian ADHD practice guidelines. 3rd edition. Toronto (ON): CADDRA; 2011.
58. Senderey E, Sousa J, Stavitsky M. Does quality of life outweigh the cardiovascular risks of stimulant medication in a child with ADHD and hypertrophic cardiomyopathy? BMJ Case Rep 2017;2017. https://doi.org/10.1136/bcr-2017-222072. bcr2017222072.
59. Nasser A, Liranso T, Adewole T, et al. A Phase III, randomized, placebo-controlled trial to assess the Efficacy and safety of once-daily SPN-812 (viloxazine extended-release) in the treatment of attention-deficit/hyperactivity disorder in school-age children. Clin Ther 2020;42(8):1452–66.
60. QELBREE. QELBREE™ (viloxazine extended-release capsules), for oral use Initial U.S. Approval: 2021. fda.gov. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211964s000lbl.pdf. Accessed January 25, 2022.
61. KAPVAY. Prescribing information for clonidine (Kapvay®) extended-release tablets. accessdata.fda.gov. 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022331s001s002lbl.pdf. Accessed January 28, 2022.
62. INTUNIV. Prescribing Information for INTUNIV® (guanfacine) extended-release tablets. accessdata.fda.gov. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022037s018lbl.pdf. Accessed January 28, 2022..
63. Gutgesell H, Atkins D, Barst R, et al. Cardiovascular monitoring of children and adolescents receiving psychotropic drugs: a statement for healthcare professionals from the Committee on Congenital Cardiac Defects, Council on Cardiovascular Disease in the Young. Am Heart Assoc Circ 1999;99(7):979–82.
64. O'Keefe L. ECGs for all Adhd patients? AAP-AHA RELEASE JOINT 'CLARIFICATION' On AHA recommendation. American Academy of Pediatrics. 2008. Available at: https://www.aappublications.org/content/29/6/1.1. Accessed September 28, 2021.
65. Wilens TE, Prince JB, Spencer TJ, et al. Stimulants and sudden death: what is a physician to do? Pediatrics 2006;118(3):1215–9.
66. Ekelund U, Luan J, Sherar LB, et al. Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. JAMA 2012;307(7):704–12 [Erratum appears in JAMA 2012;307(18):1915. Sardinha L [corrected to Sardinha, L B]; Anderssen, S A [corrected to Anderson, L B]].
67. Leslie LK, Rodday AM, Saunders TS, et al. Cardiac screening prior to stimulant treatment of ADHD. Pediatrics 2012;129(2):222–30.
68. Elia J, Vetter VL. Cardiovascular effects of medications for the treatment of ADHD. Paediatr Drugs 2010;12(3):165–75.
69. Fay TB, Alpert MA. Cardiovascular effects of drugs used to treat ADHD: Part 1: epidemiology, pharmacology, and impact on hemodynamics and ventricular repolarization. Cardiol Rev 2019;27(3):113–21.
70. Vetter VL, Dugan N, Guo R, et al. A pilot study of the feasibility of heart screening for sudden cardiac arrest in healthy children. Am Heart J 2011;161(5):1000–6.e3.
71. Lamberti M, Italiano D, Guerriero L, et al. Evaluation of acute cardiovascular effects of immediate-release methylphenidate in children and adolescents with ADHD. Neuropsychiatr Dis Treat 2015;11:1169–74.
72. Mahle WT, Hebson C, Strieper MJ. Electrocardiographic screening in children with ADHD. Am J Cardiol 2009;104(9):1296–9.

73. Sanchis-Gomar F, Pareja-Galeano H, Santos-Lozano A, et al. Long-term strenuous endurance exercise and the right ventricle: is it a real matter of concern? Can J Cardiol 2015;31(10):1304.e1.
74. Grasser EK, Miles-Chan JL, Charrière N, et al. Energy drinks and their impact on the cardiovascular system: potential mechanisms. Adv Nutr 2016;7(5):950–60.
75. Armstrong S, Li JS, Skinner AC. Flattening the (BMI) curve: timing of child obesity onset and cardiovascular risk. Pediatrics 2020;146(2):e20201353.
76. Institute of Medicine (US) Committee on Assuring the health of the public in the 21st Century. The future of the Public's Health in the 21st Century. Washington (DC): National Academies Press (US); 2002.
77. Hammerness P, Zusman R, Systrom D, et al. A cardiopulmonary study of lisdexamfetamine in adults with attention-deficit/hyperactivity disorder. World J Biol Psychiatry 2013;14(4):299–306.
78. Wilens TE, Zusman RM, Hammerness PG, et al. An open-label study of the tolerability of mixed amphetamine salts in adults with attention-deficit/hyperactivity disorder and treated primary essential hypertension. J Clin Psychiatry 2006;67(5):696–702.
79. Shin JY, Roughead EE, Park BJ, et al. Cardiovascular safety of methylphenidate among children and young people with attention-deficit/hyperactivity disorder (ADHD): nationwide self controlled case series study. BMJ 2016;353:i2550 [Erratum appears in BMJ 2016;353:i3123].
80. Rohatgi RK, Bos JM, Ackerman MJ. Stimulant therapy in children with attention-deficit/hyperactivity disorder and concomitant long QT syndrome: a safe combination? Heart Rhythm 2015;12(8):1807–12.
81. Wolraich ML, Hagan JF Jr, Allan C, et al. Clinical practice guideline for the diagnosis, evaluation, and treatment of ADHD in children and adolescents. Pediatrics 2019;144(4):e20192528 [Erratum appears in Pediatrics 2020;145(3)].
82. Torres-Acosta N, O'Keefe JH, O'Keefe CL, et al. Cardiovascular effects of ADHD therapies: JACC review topic of the week. J Am Coll Cardiol 2020;76(7):858–66.
83. Bellato A, Arora I, Hollis C, et al. Is autonomic nervous system function atypical in attention deficit hyperactivity disorder (ADHD)? A systematic review of the evidence. Neurosci Biobehav Rev 2020;108:182–206.
84. Toce MS, Farias M, Bruccoleri R, et al. A case report of reversible takotsubo cardiomyopathy after amphetamine/dextroamphetamine ingestion in a 15-year-old adolescent girl. J Pediatr 2017;182:385–8.e3.
85. Mosholder AD, Taylor L, Mannheim G, et al. Incidence of heart failure and cardiomyopathy following initiation of medications for attention-deficit/hyperactivity disorder. J Clin Psychopharmacol 2018;38(5):505–8.
86. Kelly AS, Rudser KD, Dengel DR, et al. Cardiac autonomic dysfunction and arterial stiffness among children and adolescents with attention deficit hyperactivity disorder treated with stimulants. J Pediatr 2014;165(4):755–9.
87. Westover AN, Nakonezny PA, Adinoff B, et al. Impact of stimulant medication use on heart rate and systolic blood pressure during submaximal exercise treadmill testing in adolescents. J Child Adolesc Psychopharmacol 2016;26(10):889–99.
88. Skinner JR, Van Hare GF. Letter to the editor–detection of long QT syndrome in the community. Heart Rhythm 2015;12(7):e67.
89. Yoon SY, Jain U, Shapiro C. Sleep in attention-deficit/hyperactivity disorder in children and adults: past, present, and future. Sleep Med Rev 2012;16(4):371–88.
90. Kaisari P, Dourish CT, Higgs S. Attention deficit hyperactivity disorder (ADHD) and disordered eating behaviour. Clin Psychol Rev 2017;53:109–21.