Published in final edited form as:

J Cardiovasc Electrophysiol. 2015 October ; 26(10): 1045–1047. doi:10.1111/jce.12744.

Attention Deficit Hyperactivity Disorder and Long-QT Syndrome: Risky Business

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Keywords

Long-QT syndrome; congenital arrhythmia; Attention Deficit Hyperactivity Disorder; stimulants; adrenergic side effect

During the past decade, the concern about cardiovascular risks of stimulant medications for the treatment of attention deficit hyperactivity disorder (ADHD) have swung from panicked worry to more reasoned reflection. Recent large epidemiological studies have reassured the scientific, medical, and patient communities that a safety signal does not exist for the occurrence of cardiac events in patients receiving stimulant therapy. In this issue of the *Journal*, Zhang *et al.* provide new data on a previously understudied population in this arena, patients with the long-QT syndrome (LQTS).¹ Will the pendulum swing again?

Cardiovascular risk of ADHD medications

Stimulants have been used for decades to treat successfully ADHD. These drugs are generally well tolerated with only mild side effects.^{2, 3} Numerous trials have shown statistically significant but incrementally small increases in heart rate and blood pressure in patients on stimulants versus placebo.^{2, 3} These changes are explained by the sympathomimetic and catecholaminergic effects of the medications. Arrhythmias are an extremely rare adverse event.

Concern about the cardiac safety of stimulants and their potential association with sudden cardiac death began in 2006 when FDA compiled reports from its Adverse Event Reporting System (AERS). The actual number of cases reported was small (25 people taking ADHD medications died suddenly) but the AERS is a voluntary reporting system and likely represents a fraction of actual events.⁴ Notably, a substantial subset of patients who experienced sudden death had an underlying structural cardiac abnormality on autopsy or other potential susceptibility factor. Following these reports, regulatory agencies took a number of actions including Health Canada temporarily suspending the sale of Adderall XR

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Dr. Berul: No disclosures.

and the FDA requiring the addition of a black box warning for possible cardiovascular risks of stimulant medications used to treat ADHD.⁵ These actions were in turn followed by an awkwardly written American Heart Association (AHA) Scientific Statement that was widely interpreted to endorse systematic ECG screening of children and adolescents who were on or being considered for medication to treat ADHD in an effort to identify covert cardiac disease and prevent sudden cardiac death.^{5, 6} The amplitude of concern had reached its maximum. This AHA statement was subsequently clarified in a news release, but the floodgates had been opened. In an effort to calm patients and families, and clarify recommendations for providers other organizations including the American Academy of Pediatrics Section on Cardiology and Cardiac Surgery, American Academy of Child and Adolescent Psychiatry, and Canadian professional societies released statements highlighting the lack of evidence to support widespread screening and recommended that patients receive ADHD therapy without routine pre-medication ECG screening.⁷⁻⁹

As is often the case, the level of worry escalates out of proportion to the level of supporting evidence. The pendulum began to swing back toward reasoned reflection with the release of population-based data. Some of the initial data actually seemed to support the level of worry. A matched case-control study identified a significant association between sudden death and use of stimulants for ADHD.¹⁰ A group of children and adolescents who experienced sudden unexpected death were compared with a group of age matched controls who had died in motor vehicle accidents. The individuals who died suddenly were found to have used stimulants (1.8%) more frequently than the controls (0.4%). This striking difference however was confounded by critical limitations including recall bias, incomplete data ascertainment, inadequate matching procedures, and small sample size.² One could even argue that the 1.8% rate is similar to the rate of ADHD prescription stimulant use among all children, so that no causality can be shown.

From 2007 to 2012, several large epidemiologic studies were published evaluating the potential association of stimulant medications with sudden death and cardiovascular events.¹¹⁻¹⁶ These studies used a variety of source data including computerized health records from health plans, administrative datasets, and Medicaid claims records, capturing hundreds of thousands of person-years of follow-up of patients in the United States and United Kingdom. These studies did not identify an increased risk of sudden death or serious cardiovascular events associated with the use of stimulant medications. The large scale and consistent findings of these studies seemed to quiet the concern over the cardiac safety of stimulants. In fact, by 2012 only a minority of pediatricians and child psychiatrists were routinely obtaining ECGs prior to starting ADHD medications.^{17, 18}

ADHD medications, LQTS, and cardiovascular risk

In this issue of the *Journal*, Zhang *et al.* add to this body of literature by evaluating the risk of cardiovascular events associated with the use of ADHD medications (mainly stimulants) in a previously understudied population, patients with congenital LQTS.¹ This is an important population to study because the early case reports from the AERS implicated potential cardiac risk factors as predisposing elements that mediate sudden death associated with stimulant medications. The LQTS, characterized by catecholaminergic induced torsade

de pointes, cardiac arrest, and sudden death, may certainly be such a predisposing risk factor.

A case-control design was nested within the Rochester-based LQTS Registry to compare LQTS patients treated with stimulant or non-stimulant ADHD medications with a control population of age-, gender-, and QTc-duration matched LQTS patients who were not taking ADHD medications. The case and control groups had essentially equivalent features at baseline. During a period of nearly 8 years of follow-up, 35% of patients on ADHD medications had cardiac events compared with 16% of controls. The event rate was driven by the greater number of syncopal events in the ADHD treatment group since cardiac arrest and LQTS death were rare and equivalent between groups. After controlling for β -blocker use and prior cardiac events, patients treated with ADHD medications had a 3 times greater likelihood of having an event (mainly syncope). This risk was 6-fold in male LQTS patients taking ADHD medications. There was insufficient power to differentiate the safety of stimulant vs. non-stimulant ADHD medications, and so they were combined together.

The authors conclude that patients with LQTS who are being treated with ADHD medications have a higher risk for cardiac events. This clinical conclusion nicely aligns with physiologic expectation. Most ADHD medications have sympathomimetic side effects (demonstrated in this study by an increase in mean heart rate compared to control during follow-up) and such effects are known to predispose patients with LQTS to cardiac events. This seems a logical interpretation and overall we agree.

However, a modest degree of skepticism is deserved based on the inherent weakness of the study design – how do we really know the case and control groups are equivalent? First, at face value we know the groups are different based on two very important characteristics: one being the exposure to ADHD medication and the second is the fact that the cases all have an underlying neurobehavioral abnormality, ADHD. Patients with ADHD have autonomic abnormalities.¹⁹ In the context of LQTS, could this lead to an increased risk of syncope? The authors rightly identify this limitation within the manuscript but note that the pre-medication event rates are similar between the two groups. This leads to the second issue around equivalence. While the pre-medication event rates are similar, it is notable that post treatment with ADHD medication the event rate in the ADHD subjects increases from 25% to 35% and at the same time the event rate in control subjects decreases from 24% to 16%. While individual cardiac events are not fully dependent on preceding events, we know that they are highly correlated (an important risk factor for a cardiac event in LQTS patients is a preceding event²⁰) and thus it might be reasonable to ask what happened in the control group to reduce the number of follow-up events. Is compliance with medications and recommended LQTS situation-avoidance equivalent in ADHD vs. non-ADHD patients? Finally, as in all case control studies, it is possible that unmeasured confounding biased the effect estimates.

Clinical and public health implications

These minor quibbles should not detract from the important findings of this well-designed study. A more critical evaluation is warranted of the potential implications of this study. In

particular: (1) should patients with known LQTS and ADHD be treated with ADHD medications? And (2), should we attempt to identify the LQTS pre-symptomatically in patients with ADHD prior to starting ADHD medications?

The wise adage that we should treat each patient as an individual seems an appropriate response to the first question. Untreated ADHD has significant consequences for patients and families and can result in poor academic outcomes, increased substance abuse, and even an increased risk for motor vehicle accidents.⁷ This is to say nothing of the poor health related quality of life that these patients experience.²¹

A patient with LQTS and ADHD should have a well thought through therapeutic plan coordinated by the cardiologist and ADHD treating physician. This might include an initial trial of non-pharmacotherapy such as behavioral therapy.²² If medications are needed, as Zhang *et al.* suggest, using the lowest effective dose should be the goal.¹ The present study could not assess the safety of non-stimulant medications in LQTS due to insufficient number of patients on these drugs. Concomitant therapy with β -blockers, shown to be protective in this population, should also be strongly-considered, and reminders of recommendations to avoid other QT-prolonging medications and situations (such as dehydration and electrolyte derangements) should be frequently reinforced. While this study showed an increased rate of syncope in the ADHD treated group, it is well known that syncope may be a harbinger of additional, more severe events in patients with the LQTS²⁰. Therefore, patients with LQTS who are receiving ADHD medications should be closely monitored. Episodes of syncope should be aggressively investigated and may necessitate a re-evaluation of the current treatment plan for both the ADHD and the LQTS.

The broader question of whether ADHD patients should be screened for LQTS prior to initiating medications has major public health implications. Such an effort would likely involve widespread ECG screening of patients to identify those with prolonged QT intervals. This harkens back to the AHA Scientific Statement that advocated for consideration of using the ECG as part of the pre-medication cardiac evaluation.

It is our opinion that the current findings by Zhang *et al.* should not alter the current consensus that widespread ECG screening is not required prior to starting ADHD medications. In particular, the current study does not modify the two underlying concepts that argue against the utility of widespread screening. First, the best epidemiological data available suggest that the incidence of sudden cardiac death and other cardiac events in association with ADHD medications is rare and likely no higher than the background rate of the general population. The present study does not demonstrate any difference in sudden death rate – only the combined event endpoint that is predominantly syncope. If the goal of ECG screening is to reduce the incidence of sudden cardiac death, then within this context, the barriers to success would be impossibly high. Second, the ECG is a very inefficient tool for identifying patients with a rare disease, such as the LQTS. Estimates of prevalence range from 7 to 40 per 100,000.²³ Rodday *et al.* demonstrate that whether maximizing for accuracy or specificity in a screening context, the positive predictive value of the ECG remains very low (0.04% to 0.7%) with a prohibitively high number need to screen to identify one case of LQTS (16,000 to 135,000).²³ Using the high end prevalence estimates

improves these parameters only modestly. Further, several studies have questioned the cost-effectiveness of ECG screening as a strategy to reduce the incidence of sudden cardiac death associated with ADHD medication.^{24, 25}

The pendulum of concern over the cardiovascular risk associated with ADHD medications has swung from one extreme to the other and now rests at reasoned reflection. The findings of the current study should not disturb that equanimity. Zhang *et al.* have identified patients with the LQTS as a potentially higher risk subgroup within the much larger ADHD population.¹ Their measured conclusions suggest an individualized, attentive, and judicious management strategy for these patients. However, this high risk group has a sufficiently rare prevalence that changes to current public health prevention strategies are not warranted.

Acknowledgments

Dr. Kaltman is a full-time employee of the National Heart, Lung, and Blood Institute, which provided partial funding support for the article that is the subject of this editorial. The views expressed in this editorial are those of the author and do not necessarily reflect those of the NHLBI, the National Institutes of Health, or the U.S. Department of Health and Human Services.

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