A Comparative Meta-Analysis of Cardiovascular Risk During the Treatment of Adult Age ADHD with Mixed-Salt Amphetamine and Methylphenidate Compounds

By

Nicholas Hill

Research Project

Submitted to the Department of Health and Human Sciences

Eastern Michigan University

in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

in

Clinical Research Administration

Submitted to:

Irwin Martin, PhD

21 February 2018

Ypsilanti, Michigan

Abstract

Generally, most physicians accept that first-line treatment of adult attention deficit hyperactivity disorder (ADHD) is the prescription of psychostimulant medications. These medications generally fall into two broad categories; methylphenidates (METs), part of the piperidine and phenethylamine classes, and mixed-salt amphetamines (mAMPs), which belong to the phenethylamine class. METs are believed to be effective in managing ADHD by inhibiting the reuptake of dopamine and norepinephrine in the post-synaptic cleft. AMPS also inhibit the reuptake of dopamine and norepinephrine, and in addition cause an increase in the release of the two neurotransmitters in the post-synaptic cleft. Considering ADHD is believed to be caused by both a deficit in dopaminergic transmission in the mesocorticolimbic projection and a second deficit in norepinergic transmission in the locus coeruleus, this explains the efficacy of both medications in treating ADHD. Although both medications have been studied extensively independently, there is a dearth of literature in comparing the two psychostimulants in regards to the risk that each drug offers from a cardiovascular standpoint. This lack of comparison to some degree hampers the development of a treatment plan that minimizes risks specific to each patient. In an age that has made its primary approach to medicine a personalized one, developing individualized care is becoming more and more of a necessity for optimal clinical outcomes. This meta-analysis looked at the difference in cardiovascular risk between mAMPs and METs and found differences in adverse events reported for each, as well as slight differences in labeling, but unfortunately neither difference could be reinforced by literature review. This meta-analysis found primarily that there needs to be more research done in adult populations and their usage of both drugs to substantiate whether a difference in cardiovascular risk exists between the two drugs or not.

Table of Contents

List of Figures

List of Tables

Table Page

Introduction and background

Epidemiological considerations and criteria for diagnosis

In the United States, it is estimated that 4.4% of the population aged 18-44 has Attention Deficit Hyperactivity Disorder (ADHD) (Kessler et al., 2006). This equates to roughly 5 million adults, of which less than 20% will ever seek any form of treatment (Newcorn, Weiss, & Stein, 2007). ADHD in adults is associated with a host of difficulties in day-to-day functioning and is recognized by the Diagnostic and Statistical Manual of Mental Disorders – 5th edition (DSM-5™) to present in several forms. Each one of these forms is further divided into three different levels of severity (American Psychiatric Association, 2013).

Presentation of ADHD may be primarily inattentive, which is characterized by: a failure to give close attention to detail, difficulty in sustaining attention in tasks or activities, a failure to listen when spoken to, a failure to follow through with instructions, a failure to finish workplace or schoolwork assignments, difficulty with the organization of tasks and activities, a reluctance or dislike of participating in activities that require continuous mental effort, a persistent inability to keep track of things, easily distractible by extraneous stimuli, and a persistent pattern of forgetfulness (American Psychiatric Association, 2013). ADHD may also be primarily hyperactive and impulsive, which is characterized by: fidgeting, inappropriate feelings of restlessness, an inability to engage in activities quietly, excessive talking, and impulsive behavior, such as interruptions, recklessness, and poor decision-making skills (American Psychiatric Association, 2013). These two types also sometimes present in a so called "combined type" with some individuals. This combined type consists of a mixture of features from both primary types (American Psychiatric Association, 2013).

The three recognized types also present in different levels of severity. These levels may be mild, moderate, or severe. Mild severity usually results in minor functional and social deficits. At the other end of the spectrum, the most severe level of presentation is characterized by a clear deficit in functional and social operation. Moderate severity falls in between the two extremes (American Psychiatric Association, 2013). For the formal diagnosis of ADHD to be made, an individual must present with at least six of the previously mentioned symptoms for a period of longer than six months; severity is usually judged at diagnosis (American Psychiatric Association, 2013).

ADHD is most commonly diagnosed in childhood and this diagnosis sometimes becomes no longer applicable with the transition into adulthood. Per Kessler et al. (2005) however, 36.3% of those with a childhood diagnosis of ADHD will carry this diagnosis into adulthood. This persistence into adulthood is often accompanied by comorbidities that make daily functioning even more difficult for adults that do not seek treatment (Newcorn et al., 2007).

In regards to the diagnosis of ADHD in childhood, it is also worth noting that there exist racial and ethnic disparities in the rate of diagnosis. Per Morgan, Staff, Hillemeier, Farkas, and Maczuga (2013), African American, Hispanic, and other non-white children beginning in kindergarten through the eighth grade, were 69% less likely to be diagnosed with ADHD. Also worth noting in this regard, is that non-white children that did receive a diagnosis of ADHD were less likely than white children to receive pharmacologic intervention (Morgan et al., 2013). This is a significant difference in both the diagnosis and treatment of ADHD between whites and other ethnic groups that is not adequately explained by confounding factors and is worth mentioning for epidemiologic background.

Etiology and neurological considerations

The etiology of ADHD is currently accepted to be one of both a genetically acquired and an environmentally influenced nature (Curatolo, D'Agati, & Moavero, 2010). In terms of genetic susceptibility, it is believed that at least the genes SLCA3, DRD5, DRD4, and SNAP-25 are implicated in the pathogenesis of ADHD (Curatolo et al., 2010). In addition, ADHD has also been linked to the chromosomal regions 6q12, 17p11, 16p13, and 5p13 (Ogdie et al., 2004). Individuals with ADHD also show a rather rare trend in terms of genetic considerations. This trend is usually associated with neurodevelopmental disorders and is called copy number variants (CNVs). CNVs are large chromosomal deletions and duplications and their presence alters many base pairs at once, thus allowing for a disease phenotype to be expressed or recessed in an individual (Williams et al., 2010).

Although the heritability of ADHD has been deemed to be as high as 76% (Faraone et al., 2005), genetics alone is usually not the only factor at play for ADHD to develop. Indeed, there have been multiple environmental factors implicated in the pathogenesis of ADHD as well. These environmental factors fall into prenatal and postnatal categories and very broadly speaking, range from fetal exposure to alcohol or tobacco (Sen & Swaminathan, 2007) to malnutrition, resulting in a deficiency of essential fatty acids, particularly omega-3/-6 (Colter, Cutler, & Meckling, 2008).

In terms of what's happening on a neurological basis in people with ADHD, there are believed to be multiple distinct cellular mechanisms involved. Individuals with ADHD show deficits in both the dopaminergic and norepinergic neurotransmitter systems (Chandler, Waterhouse, & Gao, 2014). These deficits particularly affect neurotransmission in pathways originating in the ventral tegmental area (VTA) and locus coeruleus (Chandler et al., 2014). Both

the VTA and the locus coeruleus pathways are implicated in a variety of cognitive processes, including attention. These dopaminergic and norepinergic pathways also project to the striatum and the prefrontal cortex. These pathways have a large role in what is generally considered executive function. This includes processes such as motivation, reward processing, and control of behavior (Malenka, Nestler, & Hyman, 2009). Children diagnosed with ADHD also show differences in brain volume when compared to controls and these differences generally correlate to a reduction in volume of the left prefrontal cortex and the posterior parietal cortex (Krain & Castellanos, 2006). All of this evidence supports a strong basis for the biological development of ADHD.

Pharmacologic treatment options

For adults that do seek treatment, ADHD is generally treated with one of several classes of medication, the administration of which is sometimes accompanied by behavioral therapy. Very broadly, the two categories of medications used to treat ADHD are Central Nervous System (CNS) stimulants and non-stimulants. Non-stimulants and stimulants both are generally divided further into different classes. For the non-stimulants, these classes include: norepinephrine reuptake inhibitors (NRIs), alpha-2 adrenergic receptor agonists/imidazoline receptor agonists (A2RA/IRAs), and selective alpha-2 adrenergic receptor agonists (sA2RAs). These medications have distinct mechanisms of action (MoAs) and work in a different manner than stimulants. They are worth mentioning for background reference to the different treatment options available for ADHD for patients in which stimulant administration is contraindicated.

Stimulants on the other hand, are generally divided into two classes the two most commonly prescribed of which are methylphenidates (METs) and amphetamines (AMPs). Stimulants are considered first-line in the treatment of ADHD and they are considered by far the

most effective intervention, with a response rate of up to 76% (Spencer et al., 2004). METs fall into the pharmacologic piperidine and phenethylamine classes, while AMPs fall into the phenethylamine class. Both drugs have distinct MoAs unique to their chemical structure.

METs work by inhibiting the reuptake of dopamine and norepinephrine in the CNS, thus addressing the deficit of the two neurotransmitters in those with ADHD. Specifically, METs inhibit the dopamine transporter (DAT) and the norepinephrine transporter (NET), causing an increase in the concentration of both catecholamines in the post-synaptic cleft (Markowitz & Kennerly, 2008). METs are also thought to increase neuronal firing rate (Viggiano, Vallone, & Sadile, 2004) and administration of MET is believed to lead to an elevation of extracellular dopamine and norepinephrine that is 3 to 4 times higher than baseline concentration (Heal and Smith). METs are also weak 5-HT agonists, which differentiate them significantly from the pharmacologic profile of AMP. The dextrorotatory enantiomer of MET, termed dexmethylphenidate (dMET), is also prescribed for the treatment of ADHD and operates through the same MoA as MET, but demonstrates a two-fold potency for DAT and NET when compared to MET (Chavez, 2015).

AMPs on the other hand, work through inhibiting the reuptake of dopamine and norepinephrine in the CNS. Different than MET however, AMPs have an additional chemical action that causes a substantial increase in the release of the two neurotransmitters. AMPs are thought to be transported into neurons by DAT or to diffuse directly across the neuronal membrane. Once absorbed into the neuron, AMPs act as full agonists of the trace amine-associated receptor 1 (TAAR1) (Miller, 2011). Activation of TAAR1 by AMP inhibits monoamine reuptake through phosphorylation of DAT, which causes the receptor to be internalized (Miller, 2011). AMPs also affect the function of vesicular monoamine transporter 2

(VMAT2). When AMP is absorbed presynaptically, it causes the vesicular pH gradient to collapse and this in turn causes the release of synaptic vesicles carrying dopamine (Eiden & Weihe, 2011). AMPs are believed to have a similar MoA involving the same receptors with regards to their effect on norepinephrine release and reuptake inhibition (Miller, 2011). Unlike METs, AMPs slow neuronal firing rates via activation of TAAR1. (Ledonne et al., 2011). In terms of stereoselectivity, dextroamphetamine (dAMP) is between three to four times more potent of a TAAR1 agonist, while levoamphetamine (lAMP) has a more potent effect on peripheral nervous system stimulation (Miller, 2011).

Both METs and AMPs exist in various dosage forms tailored to fit both pediatric and adult patients. METs exist in 13 different dosage forms that range from oral liquid to patch to capsule to tablet to orally dissolving tablet (FDA 2018). These dosage forms also exist in both immediate release and extended release preparations and vary by milligram strength from product to product. AMPs on the other hand, exist in racemic mixtures, pure dAMP forms, prodrug formulations, and mixtures of dAMP and lAMP with different salt components that affect release time and bioavailability. These dosage forms range from capsule to tablet to liquid and similarly to METs, vary considerably by milligram strength and release time.

Cardiovascular considerations

AMPs and METs are not the perfect treatment for ADHD; as with any drug, their usage carries both potential therapeutic benefit and risk. These risks were deemed significant enough that in 2006, the FDA ordered a so-called “black box” warning be added to the labeling of all psychostimulants, including AMPs and METs. This warning states that “sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problem(s)” (Smith, 2006).

Considering the FDA's ordered change in labeling, one of the primary concerns in terms of risk for both drug classes is the potential for the occurrence of adverse cardiovascular events. Stimulants are known for their ability to cause sympathomimetic effects and indeed, this is what lends them their therapeutic efficacy. Unfortunately, this sympathomimetic tendency is also what causes most of the side effects that occur with both AMPs and METs (Westfall, 2009). On average, METs raise blood pressure (BP) by 2-4 mmHg and heart rate by 3-6 beats per minute. METS' cardiovascular events may include: palpitations, both increases and decreases of BP and pulse, tachycardia, arrhythmia, and angina (Novartis Pharmaceutical Corporation, 2017). METs also carry more serious warnings for adults including: sudden death, stroke, and myocardial infarction (MI), although these risks are potentially linked with preexisting serious cardiac conditions (Novartis Pharmaceutical Corporation, 2017).

AMPs on the other hand, have cardiovascularly pertinent side effects that include: palpitations, elevation of BP, tachycardia, and cardiomyopathy (Teva Pharmaceuticals USA Inc, 2016). AMPs also carry more serious risks including: sudden death, MI, and stroke. Like METs however, some of this risk is likely associated with preexisting cardiac conditions. In examining both drugs prescribing information, it is clear there is a need to evaluate several factors: how common the risk of a serious adverse cardiac event occurring in an adult population is, if one drug represents a substantially safer therapeutic option over the other, and whether one population is substantially more affected by this risk. This was the primary subject of concern for this meta-analysis.

Purpose

The purpose of this meta-analysis was to determine whether there is a substantial difference in the cardiovascular risk between METs and mixed-salt amphetamines (mAMPs) in

treating adult age ADHD. This includes an examination of both drug classes, the frequency of cardiovascular adverse events (AEs) in both classes, their use in different populations, whether this risk/benefit profile changes in different populations, and whether this difference has implications for clinical outcomes.

Secondary objectives

Secondary objectives for this analysis included: examining long-term use data for METs and mAMPs and discussion of any difference in cardiovascular risk found over time, and a brief examination of the occurrence of non-cardiovascular serious adverse events (SAE) with routine therapeutic use of either METs or mAMPs.

Methodology

Literature review

The assertions made in this meta-analysis were primarily the result of analyzing existing literature. Screening criteria for the inclusion of literature in this project was that the material must have been: a) peer-reviewed, b) published in a prominent and reputable medical or scientific journal or other reputable medium, and c) could stand up to rigorous evaluation when examined from a statistical and methodological standpoint. Case studies were not included both because they do not contain the statistical power of population studies and because they often involve multiple comorbidities that are not possible to control for. Additional criteria for literature to be included: articles must focus on adults aged 18 and up, subjects' length of participation must be a minimum of six months, sample sizes must have been a minimum of 200 individuals, statistical significance must have been $p \leq 0.05$, and administration of drug must have been limited to approved labeling. Trends from the literature were examined to strengthen any cardiovascular safety differences found between the two compounds. There was also an analysis of existent literature that examined both types of psychostimulants. Searching for articles was performed using the following databases: Pubmed, CINAHL, Google Scholar, Medline, JAMA Cardiovascular Toxicology, and the Journal of Psychopharmacology. Keywords used for searching included: Adult, Adderall, ADHD, Ritalin, Cardiovascular, Risk, Myocardial Infarction, Methylphenidate, Mixed-salt Amphetamine, Dextroamphetamine, Amphetamine, Concerta, Adderall XR, Long Term, Safety, and Heart.

FDA adverse event reporting system (FAERS)

Data from the publicly available FAERS was also incorporated into this meta-analysis for an examination of the cardiovascular AE and SAE profile for both drugs. AEs and SAEs were examined by specific cardiovascular type, level of seriousness, and strength of correlation. FAERS data were not used unless existent literature could support at least a potential causal connection between the event and drug administration. In other words, the event had to at least be plausible based on available approved labeling information for its inclusion in this analysis. Data used from FAERS were obtained from: https://fis.fda.gov/sense/app/777e9f4d-0cf8-448e-8068-f564c31baa25/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis. These data were assessed on 07 January 2018.

Comparison of labeling information

Labeling information was compared between METs and mAMPs. Labeling was evaluated for general differences in safety and most common side effects. Special consideration was given to cardiovascular events and a comparison was made between labeling information and FAERS data in terms of reported adverse events. This was aided in part by ClinicalKey's Clinical Pharmacology website, which acted a resource in determining the frequency of adverse events in clinical practice (Elsevier Inc, 2018).

Definitions

"MET" was defined as Methylphenidate Hydrochloride immediate release formulation (proprietary name Ritalin®) for FAERS data. For literature review, both the immediate release and extended released formulation (proprietary name Concerta®) were used because of the dearth of literature on just the immediate release formulation. "mAMP" was defined as a

Dextroamphetamine Sulfate, Dextroamphetamine Saccharate, Amphetamine Sulfate, Amphetamine Aspartate Monohydrate immediate release formulation (proprietary name Adderall®) for FAERS data. For literature review, both the immediate release and extended release formulation (proprietary name Adderall XR ®) were used because of the dearth of literature on just the immediate release formulation. “Adult” was defined as being from age 18-64 for FAERS data. “Cardiovascular event” was defined as any untoward adverse event related to heart and circulatory system function that occurred after administration of drug with a causal connection at least being a reasonable possibility. “Long term” was defined as six months or more of continuous drug administration.

Results

FAERS methylphenidate data

A search of MET by both generic and proprietary names in the FAERS database when sorted by the age of 18-64 and the reaction group cardiac disorders, yielded 851 reports from the years 2000-2017. The total number of reports for MET between the ages of 18-64 was 5842, making approximately 15% of the reported AE cases cardiovascular related. The non-cardiovascular reported events numbered 4991 of which 3546 were considered serious and 395 resulted in death. This death rate represented 7.9% of the non-cardiac events. Of the cardiac cases, 815 were considered serious and 122 resulted in death. This death rate represented 14.3% of the reported cardiac events. In comparison to all the other reported adverse event categories resulting in death, the percentage of cardiac events is nearly double. In terms of seriousness, non-cardiac disorder serious events represented 71% of the total reports. Cardiac disorder serious events represented 96% reports. The most common cardiac event for METs by far reported on FAERS was tachycardia in various forms with 314 reports. See Figure 1. The nine event types the figure displays account for 98.9% of the total reported cardiovascular events.

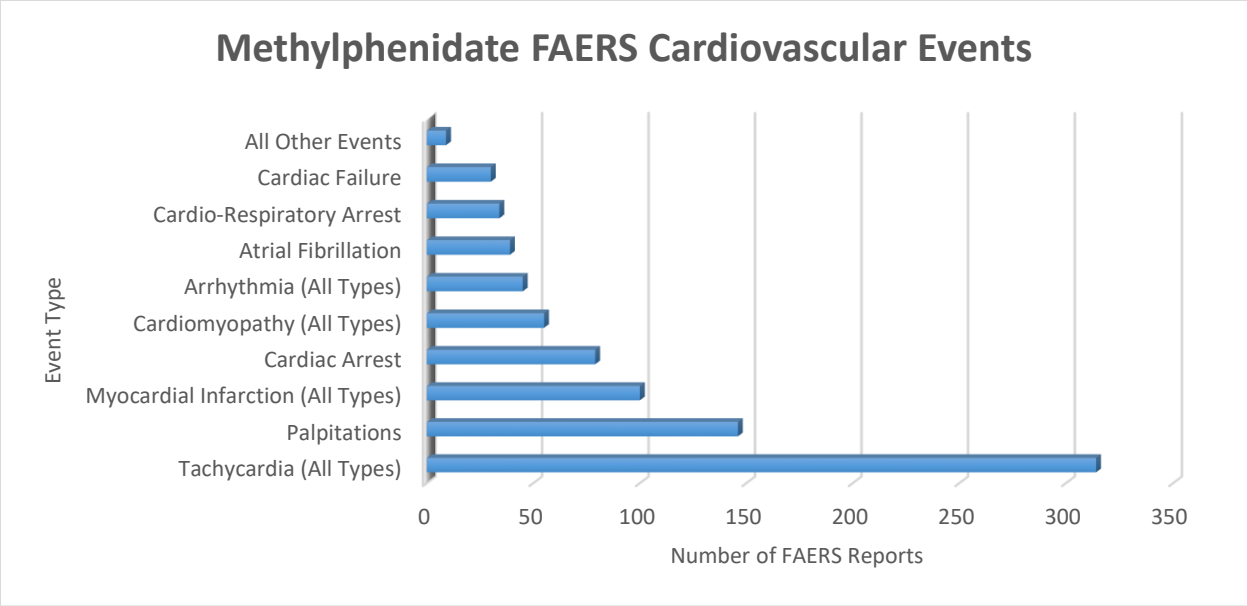

Figure 1: Methylphenidate FAERS Cardiovascular Events. Events were obtained from the FAERS database and grouped together by event type if similar in physiological effect. For example, ventricular tachycardia, sinus tachycardia, and supraventricular tachycardia were grouped as 'Tachycardia (All Types)'. The number of FAERS reports is the raw number of total reports pulled from the FAERS webpage. Tachycardia (All Types) was the highest reported AE, while Cardiac Failure was the least reported single event.

FAERS mixed-salt amphetamine data

A search of mAMP by both generic and proprietary names in the FAERs database when sorted by the age of 18-64 yielded 5479 AE reports from the years 2000-2017. Of these 723 were cardiac disorders, representing ~13% of the total events reported. Non-cardiovascular cases numbered 4756 of which 2819 were serious and 333 resulted in death This death rate represented 7% of non-cardiac cases. Cardiac disorder events on the other hand, numbered 622 serious adverse event (SAE) reports and 217 deaths, representing 35% of cardiac cases. Thus, the cardiac disorder death percentage is approximately five times greater that of non-cardiac related events. In terms seriousness, non-cardiac disorder serious events represented 59% of total

reports, while cardiac disorder serious events represented 86% of total reported cardiac disorder events. See Figure 2.

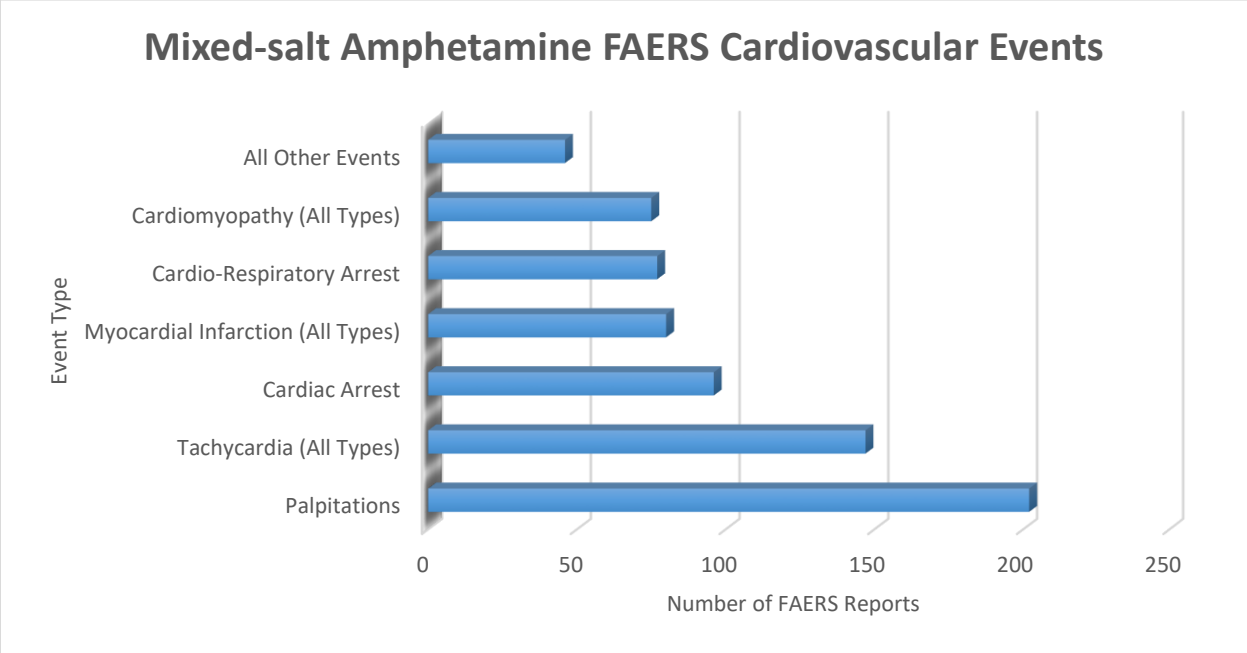

Figure 2: Mixed-salt Amphetamine FAERS Cardiovascular Events. Events were obtained from the FAERS database and grouped together by event type if similar in physiological effect. For example, congestive cardiomyopathy and generalized cardiomyopathy were grouped as 'Cardiomyopathy (All Types)'. The number of FAERS reports is the raw number of total reports pulled from the FAERS webpage. Palpitations was the highest reported AE, while Cardiomyopathy (All Types) was the least reported single event.

Comparison of FAERS data to product labeling and clinical data

Examination of the approved labeling information for both METs and mAMPs, as well as an examination of ClinicalKey's Clinical Pharmacology, a medical library for professional use that gathers clinically pertinent information about drugs, yielded differences and similarities to the AE profile found in the FAERS data. METs approved labeling included the very common (≥10%) AEs: anorexia (2-30.6%), headache 2.4-22.2%), insomnia (2-16.6%), irritability (2-11%), nausea (2.4-12.8%), vomiting (1.7-10.2%), and xerostomia (14%). It is interesting to note

that none of the most common events are cardiovascular and all of them are considered mild in terms of clinical significance. In fact, only two of the FAERS cardiovascular events appear in the infrequent (1-10%) listing of AEs; palpitations (2-3.1%) and sinus tachycardia (0.7-4.8%). Both events are considered moderate for clinical significance. In the rare (Less than 1%) listing of adverse reactions, myocardial infarction (MI) is the only cardiovascular event that is listed and it is listed as occurring with an unknown frequency of below 1% and is obviously severe in terms of clinical significance.

The most common (≥10%) AEs of mAMPs in comparison include: abdominal pain (11-14%), anorexia (22-36%), headache (26%), insomnia (12-27%), weight loss (4-11%), and xerostomia (2-35%). Just like METs, mAMPs common reactions were considered clinically mild. Also like METs, there were no adverse cardiovascular reactions in the most commonly occurring category. In the infrequent (1-10%) listing of events, palpitations (2-4%) and sinus tachycardia (6%) are again the only cardiovascular events noted. In the rare (Less than 1%) category however, there are no cardiovascular-related events listed.

It is interesting to note that between both mAMPs and METs there is an unknown category, in which the frequency of events cannot be determined. These events are usually either of extremely rare frequency, or events have not been directly attributed to the drug alone. Worth noting is that these events are usually based on single cases and whether due to rarity or undefined cause, could be more or less frequent than reported. All the other FAERS cardiovascular events for both drugs, including cardiomyopathy, cardio-respiratory arrest, cardiac arrest, arrhythmia, atrial fibrillation, and cardiac failure, fall into this category.

Literature review

Five studies met the search criteria for this section. Publications that focused on mAMP compounds were separated from those that primarily focused on MET compounds. There was a single publication that examined both medications in a "lumped together" psychostimulant generalized approach and this source was used to examine cardiovascular safety for both compounds.

Beginning with mAMP compounds, two studies that fit the criteria for population demographics were found. These two studies vary in their methodologies, population size, duration, and events of concern, but were the only studies found that focused directly on the safety profile of mAMP compounds in adult populations. In both studies, cardiovascular SAEs were found to be minimal for approved therapeutic uses of mAMPs. See Table 1. The first study done by Weisler, Biederman, Spencer, and Wilens (2005) demonstrated long-term (2 years) safety with doses of mAMP ranging from 20-60 mg per day with p-values ranging from 0.019 to <0.001 depending on the variable being measured. These variables included: diastolic blood pressure, systolic blood pressure, and pulse. A weakness of this study however, is that the sample size not large enough to provide the statistical power required (n=223). Looking at the frequency that most cardiovascular AEs seem to occur as noted in the approved labeling, it is easy to see that this analysis would require thousands of individuals to truly study the safety of mAMPs.

The study done by Schelleman et al. (2013) however, was a highly powered one (n=297,764). It also matched participants for age (bands up to six years), sex, state, and data source. What it made up for in power though, it lost in significance, as the authors themselves point out that the potential for a modest elevation in risk existed (p=0.05) because the lack of events did not allow for a stratified analysis. In addition to this flaw, the authors also admit that

this study was not randomized. In terms of raw risk numbers, the authors determined a relative risk of 1.18 for sudden death or ventricular arrhythmia and 0.75 for MI in new users compared to non-users, but did not consider this a significantly increased risk.

Mixed-salt Amphetamine Literature Summaries

Study	Author/Year	Population	Study Duration	Methods	Events Examined	Conclusion
Long-Term Cardiovascular Effects of Mixed Amphetamine Salts Extended Release in Adults With ADHD.	Weisler et al. 2005	223 Adults, ≥18 years of age.	Up to 24 months.	Participants received from 20-60mg of mAMP per day and received baseline, weekly, and monthly ECGs and examinations.	Diastolic BP, Systolic BP, Pulse, QTcB	Cardiovascular effects are minimal in healthy adults with ADHD treated with mAMPs.
Amphetamine, Atomoxetine and the Risk of Serious Cardiovascular Events in Adults.	Schelleman et al. 2013	Adults aged 18-65+, 38,586 in the mAMP group, 20,995 in the Atomoxetine group, and 238,183 in the nonuse group.	180 days before and 180 days after initiation of mAMP or Atomoxetine.	Cohort study; Used a 5 state Medicaid database and a 14 state HealthCore Integrated Research database. Comparison between mAMPs, Atomoxetine, and non-users of either drug.	Sudden Death, Ventricular Arrhythmia, Stroke, MI	Initiation of AMPs or Atomoxetine was not associated with an elevated risk of serious cardiovascular events. The authors add that with the confidence interval (p=0.05), a modest increase in event risk is not excluded.

Table 1: Mixed-salt Amphetamine Literature Summaries. Publications found using PubMed and screened using the criteria described in the Methodology section.

A search of METs also yielded two relevant studies that fit the criteria for inclusion in this analysis. Coincidentally, these studies are very like their mAMP counterparts; one of the studies was a long-term safety study and the other was a cohort study. The first study focused on

the tolerability of MET in a dose ranging manner. Adler et al. (2011) examined cardiovascular pertinent variables of diastolic and systolic BP and pulse rate over the course of treatment with escalating doses of MET for up to one year. The authors reported no SAEs of any kind. This population was larger than its counterpart, with an n=550, but as discussed above, this is still a much smaller population than is necessary to truly determine cardiovascular safety due to the rarity of these events.

Schelleman et al. (2012) also studied MET using similar methods as their mAMP study (2013). They found a relative risk of 1.8 for sudden death and ventricular arrhythmia. The authors postulate that this increase may not be accurate because it does not correlate to the administered dose of MET. The authors also speculated that lower dosages may have been prescribed to frailer patients that were already at a higher risk of these events. There was no increased risk of MI found with MET administration. The absolute risk for MET age-standardized subjects was 2.17 per thousand person-years of use in users compared to 0.98 per thousand-person years in non-users. This generated a relative risk of 1.84. See Table 2.

Methylphenidate Literature Summaries

Study	Author/Year	Population	Study Duration	Methods	Events Examined	Conclusion
Methylphenidate and risk of serious cardiovascular events in adults.	Schelleman et al. 2012	Adults aged 18-65, 43,999 in the MET group, 175,955 in the nonuse group.	180 days before and 180 days after the initiation of MET.	Cohort study; Used a 5 state Medicaid database and a 14 state HealthCore Integrated Research database. Comparison between non-users and MET users.	Sudden Death, Ventricular Arrhythmia, Stroke, MI	MET was associated with a 1.8-fold increase in risk of sudden death and ventricular arrhythmia. There was a lack of normal dose-response relationship indicating that this may not be causal.
Long-Term Safety of OROS Methylphenidate in Adults with Attention-Deficit/Hyperactivity Disorder: An Open-Label, Dose-Titration, 1-Year Study.	Adler et al. 2011	550 Adults, ages 18-65 (mean age of 39).	6 or 12 months.	Dose escalation trial that began at 36mg and ranged to 108mg or the first AE, whichever came first.	Diastolic BP, Systolic BP, Pulse	MET was well-tolerated in doses up to 108mg. No SAEs occurred over the course of those treated for 12 months.

Table 2: Methylphenidate Literature Summaries. Publications were retrieved from PubMed and screened using the criteria described in the Methodology section.

The final publication reviewed included both METs and mAMPs, as well as Atomoxetine, and Pemoline. This publication by Habel et al. (2011) was a retrospective cohort study that examined users versus nonusers, much like Schelleman et al. (2012, 2013). Data were gathered from four study sites: Tennessee Medicaid, the HMO Research Network, Kaiser Permanente California, and Optum Insight Epidemiology from 1986 through 2005. The study

examined cardiovascular SAEs and found similar rates of occurrence between those prescribed ADHD stimulant medications and those that had never been prescribed medications. Those in the mAMP portion of the user cohort the study examined demonstrated a rate of 1.03 events per 1000 person years versus those in the MET portion of the user cohort, which demonstrated a rate of 1.76 events per 1000 person years. This seems to indicate a slight difference between safety profiles, but the authors mention that when groups were adjusted for a multivariable rate ratio (RR) there was no significant difference between groups. To attempt to control for cardiovascular confounders, the authors constructed a cardiovascular risk score. This score looked at users' and non-users' medications, inpatient and outpatient diagnoses, health care utilization, and mental health conditions. The authors admitted however, even with this attempt there exist confounders that were not possible to control for, though these confounders were not mentioned specifically. See Table 3.

Combined Methylphenidate and Mixed-salt Amphetamine Literature

Summary

Study	Author/Year	Population	Study Duration	Methods	Events Examined	Conclusion
ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-Aged Adults.	Habel et al. 2011	Adults aged 25-64, 150,359 in the use group, 292,839 in the nonuse group.	1986-2005	Retrospective Cohort study. Gathered data from four different insurance "sites". Broke users into current and new use. MET accounted for 45% of current use. mAMP for 44%.	Serious Cardiovascular Events, MI, Sudden Cardiac Death, Stroke	New/current use was not associated with an increased risk of cardiovascular events. May represent a healthy user bias.

Table 3: Combined Methylphenidate and Mixed-salt Amphetamine Literature Summary. Publication was retrieved from PubMed and screened using the criteria described in the Methodology section.

Discussion

Based on the data presented here, the relative safety of MET versus mAMP is unclear. The frequency of serious cardiovascular event occurrence appears to be low in both drugs, however that low occurrence does not correlate with the level of seriousness. The FAERS data for both METs and mAMPs, showed, respectively, 14.3% and 34.9% of the reported cardiac events as lethal. There is a large difference in these two percentages, and it would appear that mAMPs are significantly more lethal when cardiovascular events do occur.

This would be straightforward, except that it fails to consider the problems that exist with FAERS. Per the FDA's website, there are several caveats that exist with the system: duplicate and incomplete reports, no evidence for drug causation, unverified information in reports, and the statement that rates of occurrence cannot be established through FAERS. Overall, these problems do not completely undermine the database's utility, but in estimating actual cardiovascular SAE occurrence, as well as determining absolute safety between METs and mAMPs, it can be used for correlative purposes only. A final problem with FAERS is the ability for literally anyone to be able to file a report to the database and the possibility for those who are filing reports may submit incorrect information. For example, Maciejewski et al. (2017), found that when drugs received media attention in the news, FAERS also received more reports of side effects for both that drug and different drugs in the same class. This is interesting because the other drugs in the same class were not mentioned by name.

A more useful approach to utilizing FAERS data might be to examine the rate of prescription sales for each drug and then calculate a relative risk based on the number of reports filed with FAERS. This approach would require access to multiple insurance databases, however, to generate an accurate profile of the patient population taking each drug. In turn, a

dissection of each FAERS report would be necessary to correlate sales data with reported AEs to rule out comorbidities and concomitant medication interactions. This approach would be more useful when differentiating METs and mAMPs profiles, but ultimately would require logistical coordination with potentially hundreds of different insurance entities or the purchase of these sales data from a third-party source.

It is also interesting to note that when compared to approved labeling and clinical use there are at least some similarities between the database and real world occurrence. With MET data, palpitations and sinus tachycardia do seem to correlate with the drug's labeling in their frequency. Both events are considered of infrequent occurrence in METs labeling, but appear to be the most frequently reported on FAERS. This suggests the frequency of reports and that of clinical occurrence is at least somewhat correlated. Also, correlative with METs' labeling was the SAE reporting of MI, which appeared as the third most reported event on FAERS. Like METs, mAMPs also showed a correlation between the "infrequent category" in labeling and the reporting rate to FAERS for both palpitations and sinus tachycardia. Even though FAERS cannot be used by itself to determine the frequency of events, it does seem like if used properly with supplemental insurance company pharmacoepidemiologic information, it could at least provide marginal utility for AE occurrence. This would, however, need to be validated on a drug-by-drug basis. The better way to obtain this data more reliably would just be to use the insurance database information directly. Thus, while FAERS is useful for making correlations, it is apparently an unreliable tool when it comes to measuring the relative safety of products.

Three of the five studies used for safety analysis of the two drugs in this report used just such insurance pharmacoepidemiologic information to create massive cohorts for each drug. All but one of the studies found no difference between non-users of ADHD drugs and users of either

METs or mAMPs. The last study that used insurance cohort information, Schelleman et al. (2012) did find a much higher hazard ratio of 1.84 when comparing users of MET to non-users. This finding correlated inversely when compared to the dosage administered, and the authors conclude that because of this, the relationship between MET administration and sudden death or ventricular arrhythmia is likely not one of cause and effect. It appears then that this study, also is not useful in determining whether one drug is safer than the other one.

After extensive analysis, it isn't that there is no significant difference in the cardiovascular safety of METs versus that of mAMPs, but it appears that this difference has not been something that has been tested thoroughly in adults. All of the studies currently published on the topic do not use a MET versus mAMP approach; they use a user versus non-user approach. In fact, it effectively appears that METs and mAMPs are treated as the same drug, even though they have different pharmacokinetics and pharmacodynamics. This type of methodological approach is especially prevalent in adult studies, perhaps because an ADHD diagnosis is less likely to be carried into adulthood.

It appears that there is at least some additional research into the pediatric administration of either drug and cardiovascular risk. There is a published study that compares METs to mAMPs in pediatrics. This study, by Winterstein, Gerhard, Shuster, and Saidi (2009), looked at a huge cohort of approximately 2 million children from the years of 1994-2004 and examined first time emergency room visits for either cardiac symptoms or disease. Between both drug cohorts they found no significant difference in emergency room admissions, but they themselves admit the need for further long-term studies that examine differences in dosage and both drugs' effects on preexisting cardiac conditions.

Conclusion

This analysis has attempted to discern whether there exists any significant difference in the cardiovascular event occurrence rate between either METs or mAMPs for the treatment of adult-age ADHD. The lack of research on the topic was an impediment to determining if such a difference exists. It further follows that there need to be several extensive cohort-based studies that compare the administration of therapeutic dosages of METs to therapeutic dosages of mAMPs for a difference in cardiovascular safety to be determined. These studies would need to be long term, control for comorbidities and concomitant drug use, and have diverse and exceedingly large (>50,000 per group) populations. In addition, these studies must be age-matched, dose-matched, and draw their data from a mixture of both commercial, as well as state insurance databases. Without this kind of research being done all that can be said of the difference between compounds in cardiovascular risk at the present is that both drugs do represent a cardiovascular risk and this risk is rare, and it is not definitive, which, if either, drug represents a greater risk.

References

Adler, L. A., Orman, C., Starr, L. H., Silber, S., Palumbo, J., Cooper, K., Berwaerts, J., & Harrison, D. D. (2011, February). Long-term safety of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder: an open-label, dose-titration, 1-year study. *Journal of Clinical Psychopharmacology*, *31*(1), 108-114. doi:10.1097/JCP.0b013e318203ea0a

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Chandler, D. J., Waterhouse, B. D., & Gao, W. (2014, May 21). New perspectives on catecholaminergic regulation of executive circuits: evidence for independent modulation of prefrontal functions by midbrain dopaminergic and noradrenergic neurons. *Frontiers in Neural Circuits*, 8(53). doi:10.3389/fncir.2014.00053

Chavez, B. (2015, August 17). New Developments in the Treatment of ADHD in Children: How the Pharmacist and Pharmacy Technician Can Impact Care [Electronic version]. .

Colter, A. L., Cutler, C., & Meckling, K. (2008, February 14). Fatty acid status and behavioural symptoms of attention deficit hyperactivity disorder in adolescents: a case-control study. *Nutrition Journal*, 7(8). doi:10.1186/1475-2891-7-8

Curatolo, P., D'Agati, E., & Moavero, R. (2010, December 22). The neurobiological basis of ADHD. *Italian Journal of Pediatrics*, 36(79). doi:10.1186/1824-7288-36-79

Eiden, L. E., & Weihe, E. (2011, January). VMAT2: a dynamic regulator of brain monoaminergic neuronal function interacting with drugs of abuse. *Annals of the New York Academy of Sciences*, 1216, 86-98. doi:10.1111/j.1749-6632.2010.05906.x

Elsevier Inc. (2018). In *Clinical Pharmacology powered by ClinicalKey*. Retrieved February 21, 2018, from https://www.clinicalkey.com/pharmacology/

Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A., & Sklar, P. (2005, June 1). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological psychiatry*, 57(11), 1313-1323. doi:10.1016/j.biopsych.2004.11.024

Federal Food and Drug Administration. (2018). *Orange Book*. Silver Spring, MD

Habel, L. A., Cooper, W. O., Sox, C. M., Chan, A. K., Fireman, B. H., Arbogast, P. G., Cheetham, C. T., Quinn, V. P., Dublin, S., Boudreau, D. M., Andrade, S. E., Pawloski, P. A., Raebel, M. A., Smith, D. H., Achacoso, N., Uratsu, C., Go, A. S., Sidney, S., Nguyen-Huynh, M. N., Ray, W. A., & Selby, J. V. (2011, December 28). ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-Aged Adults. *JAMA*, *306*(24). doi:10.1001/jama.2011.1830

Kessler, R. C., Adler, L. A., Barkley, R., Biederman, J., Conners, K. C., Faraone, S. V., Greenhill, L. L., Jaeger, S., Secnik, K., Spencer, T., Üstün, T.B., & Zaslavsky, A.M. (2005, June 1). Patterns and predictors of ADHD persistence into adulthood: Results from the National Comorbidity Survey Replication. *Biological psychiatry*, 57(11), 1442-1451. doi:10.1016/j.biopsych.2005.04.001

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, K. C., Demler, O., Faraone, S. V. Greenhill, L.L., Howes, M.J., Secnik, K., Spencer, T., Üstün, T.B., Walters, E.E., & Zaslavsky, A.M. (2006, April). The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. *The American journal of psychiatry*, 163(4), 716-723. doi:10.1176/appi.ajp.163.4.716

Krain, A. L., & Castellanos, X. F. (2006, August 1). Brain development and ADHD. *Clinical Psychology Review*, 26(4). doi:10.1016/j.cpr.2006.01.005

Ledonne, A., Berretta, N., Davoli, A., Rizzo, G., Bernardi, G., & Mercuri, N. (2011, July 4). Electrophysiological Effects of Trace Amines on Mesencephalic Dopaminergic Neurons. *Frontiers in Systems Neuroscience*, *5*. doi:10.3389/fnsys.2011.00056

Maciejewski, M., Lounkine, E., Whitebread, S., Farmer, P., DuMouchel, W., Shoichet, B. K., & Urban, L. Reverse translation of adverse event reports paves the way for de-risking preclinical off-targets. *eLife*, *6*. doi:10.7554/eLife.25818

Malenka, R. C., Nestler, E. J., & Hyman, S. E. (2009). *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* (2nd ed., pp. 315-323). New York, NY: McGraw-Hill Medical.

Markowitz, J. S., & Kennerly, P. S. (2008, June). Differential Pharmacokinetics and Pharmacodynamics of Methylphenidate Enantiomers: Does Chirality Matter? *Journal of Clinical Psychopharmacology*, 28(3). doi:10.1097/JCP.0b013e3181733560

Miller, G. M. (2011, January). The Emerging Role of Trace Amine Associated Receptor 1 in the Functional Regulation of Monoamine Transporters and Dopaminergic Activity. *Journal of neurochemistry*, 116(2), 164-176. doi:10.1111/j.1471-4159.2010.07109.x

Morgan, P. L., Staff, J., Hillemeier, M. M., Farkas, G., & Maczuga, S. (2013, June 24). Racial and Ethnic Disparities in ADHD Diagnosis From Kindergarten to Eighth Grade [Electronic version]. *Pediatrics*, 132(1), 85-93. doi:10.1542/peds.2012-2390

Newcorn, J. H., Weiss, M., & Stein, M. A. (2007, August). The complexity of ADHD: diagnosis and treatment of the adult patient with comorbidities [Electronic version]. *CNS spectrums*, 12(8), 1-14.

Novartis Pharmaceutical Corporation. (2017, January). *Ritalin/Ritalin-SR Prescribing Information*. East Hanover, New Jersey: Novartis Pharmaceutical Corporation.

Ogdie, M. N., Fisher, S. E., Yang, M., Ishii, J., Francks, C., Loo, S. K., Cantor, R. M., McCracken, J.T., Smalley, S.L., & Nelson, S.F. (2004, October). Attention deficit hyperactivity disorder: fine mapping supports linkage to 5p13, 6q12, 16p13, and 17p11. *American Journal of Human Genetics*, 75(4), 661-668. doi:10.1086/424387

Schelleman, H., Bilker, W. B., Kimmel, S. E., Daniel, G. W., Newcomb, C., Guevara, J. P., Cziraky, M. J., Storm, B. L., & Hennessy, S. (2013, January 30). Amphetamines, Atomoxetine and the Risk of Serious Cardiovascular Events in Adults. *PLOS ONE*, *8*(1). doi:10.1371/journal.pone.0052991

Schelleman, H., Bilker, W. B., Kimmel, S. E., Daniel, G. W., Newcomb, C., Guevara, J. P., Cziraky, M. J., Storm, B. L., & Hennessy, S. (2012, February). Methylphenidate and risk of serious cardiovascular events in adults. *The American Journal of Psychiatry*, *169*(2), 178-185. doi:10.1176/appi.ajp.2011.11010125

Sen, B., & Swaminathan, S. (2007, December). Maternal prenatal substance use and behavior problems among children in the U.S [Electronic version]. *The Journal of Mental Health Policy and Economics*, 10(4), 189-206.

Smith, M. (2006, August 23). Cardiovascular Safety Warning Added for Stimulants for ADHD. In *Medpage Today*. Retrieved December 15, 2017, from https://www.medpagetoday.com/Psychiatry/ADHD-ADD/3987

Spencer, T., Biederman, J., Wilens, T., Doyle, R., Surman, C., Prince, J., Mick, E., Aleardi, M., Herzig, K., & Faraone, S. (2005, March 1). A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *Biological psychiatry*, 57(5), 456-463. doi:10.1016/j.biopsych.2004.11.043

Teva Pharmaceuticals USA Inc. (2016, October). – *Dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulfate and amphetamine sulfate tablet Labeling Information*. North Wales, Pennsylvania: Teva Pharmaceuticals USA Inc.

U.S. Food and Drug Administration. (n.d.). FDA Adverse Event Reporting System (FAERS) Public Dashboard. In *U.S. Food and Drug Administration.* Retrieved February 11, 2018, from https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm

Viggiano, D., Vallone, D., & Sadile, A. (2004). Dysfunctions in Dopamine Systems and ADHD: Evidence From Animals and Modeling. *Neural Plasticity*, *11*(1-2), 97-114. doi:10.1155/NP.2004.97

Weisler, R. H., Biederman, J., Spencer, T. J., & Wilens, T. E. (2005, December). Long-Term Cardiovascular Effects of Mixed Amphetamine Salts Extended Release in Adults With ADHD. *CNS spectrums*, *10*(S20), 35-43. doi:10.1017/S109285290000242X

Westfall, T. C. (2009). Sympathomimetic Drugs and Adrenergic Receptor Antagonists. In J. Stein (Ed.), *Encyclopedia of Neuroscience* (pp. 685-695).

Williams, N. M., Zaharieva, I., Martin, A., Langley, K., Mantripragada, K., Fossdal, R., Stefansson, H., Stefansson, K., Magnusson, P., Gudmundsson, O.O., Gustafsson, O., Holmans, P., Owen, M.J., O'Donovan, M., & Thapar, A. (2010, October 23). Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis. *The Lancet*, 376(9750), 1401-1408. doi:10.1016/S0140-6736(10)61109-9

Winterstein, A. G., Gerhard, T., Shuster, J., & Saidi, A. (2009, July). Cardiac Safety of Methylphenidate Versus Amphetamine Salts in the Treatment of ADHD. Pediatrics, 124(1). doi:10.1542/peds.2008-3138