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The Effects of Long-Term Use of Stimulant Medication for Attention Deficit Hyperactivity Disorder

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A Literature Review

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Capstone Project

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Chapter 1

Introduction

Description of the problem. Attention deficit hyperactivity disorder (ADHD) is one of the most common mental health disorders in the United States. ADHD is typically diagnosed in childhood between the ages of 4 and 7. According to a 2011 United States survey by the Centers for Disease Control (CDC), ADHD effects 11% of children ages 4-17, and that number has risen an average 5% per year since 2003. The worldwide prevalence of ADHD in children is 5.29%, demonstrating a much higher incidence in the United States. The hallmark findings of ADHD are inattention, impulsiveness, and hyperactivity which lead to difficulty completing tasks, following directions, and getting along with others. If left untreated, these behaviors can significantly hinder the child's performance in school and his or her ability to be successful later in life. For this reason, clinicians frequently prescribe stimulant medications which are considered first line therapy for ADHD with or without cognitive behavioral therapy (CBT). According to the same 2011 survey, 69% of children diagnosed with ADHD were medicated for their condition. This equates to 6.1% of all children ages 4-17 in the United States. Evidence suggests that despite being a 'diagnosis of childhood', many patients with ADHD benefit from medication therapy into adulthood. Adult patients who were not diagnosed during childhood, but demonstrate ADHD behaviors may also benefit from initiation of stimulant therapy. This data demonstrates the need for healthcare providers to have a clear understanding of the effects of long term stimulant therapy when prescribing them for their patients.

Stimulant medications include methylphenidate, dextroamphetamine, and amphetamines. Common brand names include Adderall, Ritalin, Concerta, and Vyvanse. These drugs are

regulated by the drug enforcement administration (DEA) and are considered schedule II drugs. Schedule II drugs have a high potential for abuse and abuse of the drug may lead to psychological or physical dependence. The United States food and drug administration (FDA) mandates a black box warning on stimulant medications related to abuse potential and risk for cardiovascular adverse events and sudden death. This information alone raises the question: are these medications appropriate for children? In addition to the high potential for abuse, stimulants carry a side effect profile that includes depression, hypertension, stoke, sudden death, cardiomyopathy, growth suppression, insomnia, and anorexia. Despite these risks, stimulant medications are considered relatively safe and effective therapy for control of ADHD in children and adolescents. However, as the incidence of ADHD rises, practitioners are likely to see more patients on stimulant therapy well into adulthood. The purpose of this literature review is to determine the effects associated with long term use of stimulant medications for ADHD and how these effects, positive and negative, may influence future practice guidelines.

Definition of terms.

Conceptual terms. ADHD is defined by the DSM-V criteria as a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. In order to satisfy the diagnosis of ADHD several associated behaviors must be present for a prescribed period of time. This literature review favors studies regarding ADHD that adhere to this diagnostic standard. Stimulant medications refer to medications that stimulate the central nervous system and produce a sympathomimetic effect. For the purposes of this literature review the term stimulant refers specifically to the class of stimulants called the phenethylamines which is the parent class of methylphenidate and amphetamine medications. Side effects are effects that occur secondary to the primary goal of the therapy and are usually undesirable.

Operational terms. Operationally, stimulant medication refers to a group of medications designed to enhance wakefulness, alertness, attentiveness, as well as boost motivation and productivity. For the purposes of this literature review the term stimulant is inclusive of multiple unique ADHD medications including but not limited to amphetamines (Adderall), methylphenidate (Ritalin), and Lisdexamfetamine (Vyvanse). With respect to ADHD medication, the known side effects are related to stimulant medication's effects on neurotransmitters, and the sympathetic nervous system. For this review the operational definition of side effects was comprised from the most commonly investigated secondary effects associated with stimulant therapy. The side effects are sudden death, substance abuse, and other cardiovascular risk. Other cardiovascular risk may be further defined/measured as increased incidence of tachycardia, hypertension, electrocardiogram changes, and development of cardiomyopathy. When discussing long-term effects of stimulant medications long term therapy refers to any therapy lasting greater than 6 months, or long-term therapy as defined by the individual study criteria. Therapy may be initiated in childhood or adulthood. Because ADHD medications are typically prescribed on a long term basis the discussion of the effects of these medications is in reference to long term therapy unless otherwise specified.

Theoretical framework.

For the purpose of this literature review, the effects of long term use of stimulant medications are discussed in respect to Becker's health belief model. This theoretical framework assumes that patient's attitudes and actions towards health behavior are determined by four points; the severity of the potential illness, the susceptibility to that illness, the benefits of taking action, and perceived barriers to that action (Janz & Becker, 1984). ADHD is considered a neuro-cognitive disorder and as such the outcomes of treatment can be measured subjectively by

the patient's perception of effectiveness of treatment. These outcomes may also be evident in quantitative values such as test scores. This model was originally designed to examine patient's attitudes towards preventative health behavior. It may be adapted to the use of pharmacological interventions because the discussion of the long-term effects of stimulant medications plays a large role in determining the perceived benefits and barriers. Also, because of the variation in long-term ADHD prognosis, patients and providers may individualize their treatment goals based on the risks and long-term effects associated with stimulant medications. The patient's perceived severity of their ADHD and their attitudes toward stimulant medications will be augmented by the barriers to the intervention (medication side effects and cost) or lack of perceived benefits (low efficacy). This risk versus benefit analysis of treatment options falls squarely within the realm of Becker's health belief model.

PICO question

In patients with attention deficit hyperactivity disorder (ADHD) what are the effects associated with long-term use of stimulant medications? Stimulant medications have other on-label uses for conditions such as narcolepsy, binge eating disorder, and obsessive compulsive disorder. For the purposes of this literature review, the population is limited to those patients taking these medications for ADHD. The intervention of interest is the stimulant drug itself as compared to other therapy which includes non-stimulant medications and cognitive behavioral therapies, and no therapy. Alternate therapies will not be examined to determine superiority; rather date will be generated regarding the effects associated with one intervention so that consumers and health care providers may make informed decisions about their treatment options.

Chapter Two

Literature Review

Articles for this literature review were selected after careful review of the CINAHL and Medline databases as well as the clinical key database accessed through the McKee Library. An important eligibility criterion was that the article had been published in the last 5 years. Literature older than five years may be included if the study was considered a landmark study or contributed to current guidelines. The article must address ADHD independently and not concurrent to any comorbid conditions such as autism, Tourette's, or other developmental disorders. The article must discuss use of stimulant medications for the treatment of ADHD. Articles discussing side-effects of non-prescription stimulant use and or abuse were not included. Articles that addressed adult ADHD treatment and outcomes were sought out to determine the efficacy of stimulant therapy beyond childhood. Key words used were: attention deficit hyperactivity disorder (ADHD), stimulant(s), side-effects, cardiac, substance abuse, adult, and long-term effects. For the purposes of this review specific attention was paid to studies that examined cardiac risk factors, risk of sudden-death, substance abuse, and psychosocial outcomes. Because of the wide age range of patients diagnosed and prescribed stimulant medications this review included studies that addressed both pediatric and adult populations.

A search of the databases using the search term ADHD with Boolean (and) terms stimulant medication and side effects yielded a total of 459 articles published in English since 2010 with full text available. A portion of these articles were duplicates available in more than one database. Many of these articles were comparison studies demonstrating the efficacy or superiority of one stimulant versus another. These articles were not included in the literature review. This left approximately 80 articles that were eligible for the literature review including

primary research studies, case-control studies, systematic reviews, and current literature reviews. These results were narrowed down to 20 articles based on their attention to the concepts of interest; substance abuse, cardiac side effects, and adult ADHD.

Presentation of Literature

Eight of the 20 studies addressed cardiovascular implications, 7 addressed adult ADHD considerations specifically, and 4 addressed substance abuse outcomes. One study combined the concepts of interest and reported on psychosocial adversity and mortality in adults with childhood ADHD. Cardiovascular and substance abuse articles included childhood, adolescent, and adult population studies.

Stimulant Medication and Cardiac Side Effects

Cardiovascular side effects are considered to be one of the primary concerns of clinicians who prescribe stimulant medications. This is due to varied reports regarding increased incidence of sudden death during stimulant therapy, and FDA advisory committee warnings regarding the safety of stimulant use in children. However, these reports have not been substantiated by current literature. Current evidence based guidelines indicate stimulants as first-line therapy for ADHD. The literature demonstrates a steady increase in the incidence of ADHD as well as an increase in the utilization of stimulant medications for its treatment. Multiple large studies have been conducted to investigate cardiac risk factors associated with stimulant use including elevated heart rate, elevated blood pressure, and ECG changes. These factors are thought to have cumulative effects on cardiovascular health over-time. Therefore, they may be predictive of long-term adverse effects such as acute myocardial infarction, stroke, and sudden death.

Elevation in heart rate was frequently observed during initiation of stimulant therapy (within 90 minutes of administration) in children but had no statistically significant impact with data endpoints from 5 weeks to 6 months (Awudu & Besag, 2014). In sample populations of adults taking stimulant medications for ADHD, small elevations (4-10 bpm) in heart rate were documented throughout the course of the study. This resulted in a persistent but stable elevation in heart rate up to the endpoint of 2 years (Hammerness, Surman, & Chilton, 2011). A multi-age, multi-population study by Martinez-Raga, Knecht, Szerman, and Martinez (2013) similarly found marginal but statistically significant elevation in heart rate and systolic blood pressure within the first 90 minutes of stimulant administration to children. In adults, similar elevations in heart rate and systolic blood pressure were identified at multiple data endpoints from 6 weeks to 3 years. None of the studies examined dose-dependent relationships among stimulant medication and elevation of heart rate and/or blood pressure. Each of the studies accounted for standard dosing of the medication. No differences in outcomes were demonstrated in populations taking methylphenidate versus amphetamines. Three of the 8 studies discussing cardiovascular risk examined ECG changes as a primary outcome. None of the studies recorded any evidence that use of stimulant medications caused ECG changes, specifically QT elongation, at data points up to 6 months (Awudu & Besag, 2014), (Martinez-rage et al., 2013), (Hammerness et al., 2011).

Risk of sudden death was a unique outcome evaluated independent of heart and blood pressure in two of the studies (Winterstein et al., 2012), (McCarthy, Cranswick, Potts, Taylor, & Wong, 2009). Both of these studies were large population-based retrospective cohort studies. They included massive sample groups which were representative of the general population with ADHD. Neither study demonstrated an increased incidence of sudden death among patients with ADHD who were taking stimulant medication. Data from these studies did not report the length

of time the patient had been taking stimulants, so it is difficult to say if long-term use of stimulants may influence this outcome. With such large population studies it is difficult to account for covariates such as medication dose, type, and duration. However, it is reasonable to assume that the study durations of 7 and 9 years respectively would have captured any sudden deaths linked to intermediate use of stimulant medications. McCarthy et al. incidentally found an increased rate of suicide among the population of patients with ADHD compared to the general population. It is not known if suicidality is associated with the impulsivity associated with ADHD or is a side effect of medications. This study demonstrates the need for further research to determine the relationship between suicide and ADHD.

Cardiovascular complaints are among the most common subjective complaints reported by stimulant medication users. They include palpitations and fatigue. Since the aforementioned studies demonstrated very little quantitative evidence regarding stimulant mediation and cardiovascular demands, additional studies were reviewed to investigate this phenomenon. Kelly et al. (2014) examined cardiac autonomic dysfunction and arterial stiffness related to stimulant medication use in children to explore how increased sympathetic stimulation affects cardiac automaticity and vascular health. In a sample of 138 children, specialized measures were used to determine heart rate variability and pulse wave velocity (arterial stiffness). The results were adjusted for sex, race, and tanner stage and divided into affected and control groups. The results demonstrated increased heart rate variability in subjects taking stimulant medication for ADHD. The level of variability was on par with children affected by type 1 diabetes and childhood obesity. They also demonstrated increased arterial stiffness in the ADHD population. The mean duration of stimulant use was 2.79 years. There was no identifiable relationship between duration of stimulant therapy and/or dose of stimulant therapy related to hemodynamic values. This study

identified two subclinical effects of increased sympathetic tone which are known independent risk factors for cardiovascular disease. The short term nature of this study makes it difficult to assess the impact of these effects over time. These findings generate a research question to determine the long-term implications of stimulant therapy and increased sympathetic tone.

The body's response to catecholamines impacts our energy level, wakefulness, and experience of fatigue. In children taking stimulant medications, these effects have been blunted in response to exercise. Mahon, Woodruff, Horn, Marjerrison, and Cole (2012) conducted a small volunteer based study to assess how stimulant medications affect heart rate and perceived exertion. They determined that children taking stimulant medications for ADHD were likely to report lower than average levels of exertion at a given heart rate. Furthermore, heart rates of children taking stimulant medications were higher than controls at the same perceived level of exertion. The findings of this study cannot be generalized due to the small sample size; however they do provide a possible understanding of the patient's experience of palpitations and fatigue. The researchers in this study were conducting their research as part of a larger investigation into how exercise may help decrease side effects and improve motor skills in children with ADHD. The reporters may be biased in their interpretation of the data based on their investment in the outcomes of the larger study.

Substance Abuse

Two of the 4 substance abuse articles were large population based studies using national registry data. One was a smaller community sample, and the fourth was a review of current literature. The two large population based studies demonstrated an increased occurrence of substance abuse as defined by DSM-IV criteria in patients with a diagnosis of ADHD. Of the large studies, one contained follow-up up to 15 years, while the other ended at four years. The

four-year study targeted a previously determined high risk age group at a mean age of 16.4 years. Not only were children with ADHD more likely to develop a substance use disorder, they had a younger age of first substance use, and nicotine dependence than controls. This study did not investigate how stimulant medication for ADHD influenced ADHD symptoms or propensity for substance use disorders (Groenman et al. 2013). The second study by Chang et al. (2014) examined rates of substance abuse among patients with ADHD based on current, former, or never use of stimulant medications. Because of their access to prescription databases they were also able to trend duration of therapy and correlate periods of non-use with other records including criminal convictions or hospital visits. Results were published controlling for age, sex, and medication status in 2009 (the data point of interest). Their results demonstrated that stimulant medications did not increase the incidence of substance abuse in patients with ADHD. Furthermore, there was a protective effect of stimulant medication where there was an inverse relationship between duration of stimulant therapy and rate of substance abuse. These findings are useful to practice because of the large sample size and the comparison of the intervention within the ADHD population versus the general population. Data is limited because of the severe nature of the substance abuse cases identified by criminal or hospital data. Less severe cases of substance abuse may be under-represented resulting in skewed data. Further controlled trials would be ideal to collect more sensitive reliable data, however conducting such a study would be unethical.

The review of literature and the small community based study supported the previous research stating that 1) A diagnosis of ADHD in childhood is associated with an increased risk for substance abuse and nicotine dependence. 2) The use of stimulant medications in childhood is not associated with increased long-term risk of substance abuse. The literature review posits

that current evidence is support enough for providers to feel comfortable in prescribing stimulant medications for ADHD so long as there is appropriate assessment of substance abuse behaviors, consistent follow-up, and education about the course of therapy (Nelson, & Galon, 2012). Winters et al. (2011) pose a more interesting theory based on their findings suggesting that the protective benefit of stimulant medication for ADHD with respect to substance abuse are not carried forth past adolescence. Therefore, adults who are prescribed stimulant medications may represent a unique subset when it comes to propensity for substance abuse. This theory requires further research to determine outcomes in this specific population.

Adult ADHD

ADHD is no longer a diagnosis of childhood. Its effects including inattention and impulsivity have far reaching consequences if not adequately addressed in childhood. Research suggests that primary care provider's attitudes towards adult ADHD impact their ability and willingness to prescribe both stimulant and non-stimulant therapies. Even in the absence of negative views of adult ADHD only 57.5% of providers in a small convenience sample were confident in treating adult ADHD (Martinson & Tang, 2010). Two studies examined quality of life measures in adults with ADHD. A systematic review of literature looked at the metrics used to determine quality of life in adults with ADHD and how ADHD symptoms impacted these scores. The use of established validated tools for measuring quality of life make the results of this review significant in terms of providing quantitative and reliable data. According to Agarwal, Goldenberg, Perry, and Ishak (2012), adults with ADHD demonstrate lower overall quality of life scores than the general population. Furthermore, they experience anxiety, depression, and daytime sleepiness more commonly than non-ADHD adults. Other significant areas of dissatisfaction included decreased emotional control for women, and decreased social

functioning in men. Specific treatment goals would require individualized assessment of barriers to optimum functional status. However, multiple studies reported that the use of stimulant therapy improved vitality, social, emotional, and physical well-being after 10 weeks of treatment. These findings suggest that treating ADHD itself decreased the prevalence of comorbid psychological conditions and improves overall quality of life.

Outcomes affecting quality of life include occupational success, economic stability, educational attainment, and marital history. These elements significantly influence lifelong social functioning and success. For this reason, Klein et al. (2012) examined the relationship between childhood ADHD and adult functional status. A prospective study followed 135 Caucasian males with ADHD from childhood and compared them to a demographically similar control group. They found that adults who suffered from ADHD in childhood received 2.5 years less education, and had lower levels of occupational achievement. These two outcomes produced an understandably lower socioeconomic status. Similar to the study by Agarwal et al. (2012) the population with childhood ADHD had higher rates of adult substance abuse and nicotine dependence that the general population. Klein et al. suggested that their findings indicated the importance of treatment of childhood ADHD. However, because their study did not examine outcomes based on treatment, further studies are required before specific recommendations can be made. Pitts, Mangle, and Asherson (2015) further quantified these findings using an ADHD impairment and symptoms scale which was completed by a sample of 210 adults (mean age 32). Similarly, the results showed greater difficulties in social functioning, personal relationships, personal finances, mood/temper control, self-organization, and planning, and rule breaking behavior among the population with ADHD.

ADHD can have devastating effects on adult functional status. Two of the studies investigated ADHD in older adults (>50) to grasp the full spectrum of impairment caused by adult ADHD. Brod, Schmitt, Goodwin, Hodgkins, and Niebler (2011) conducted interviews to collect data from 24 adult patients with ADHD, average age 66. None of the patients were diagnoses with ADHD in childhood, and all were diagnosed at age 30 or greater. Participants voiced impairment with managing finances, including inadequate retirement funds, as well as difficulty maintaining relationships with family and friends. The quality of life score for older adults with ADHD demonstrated the greatest discrepancy in perception of life productivity. Surprisingly, 79% of the participants were currently taking ADHD medication. They reported improved focus and attention since being on the medication. The researchers believe this small pilot study highlights the value of diagnosing and treating ADHD in patients of every age. These findings are obviously limited by sample size and largely qualitative nature of data collection. Lensing, Zeiner, Sandvik, and Opjorsmoen (2015) specifically studied pharmacology for ADHD in the older adult, mean age 55.8. Surprisingly, 87.9% of the sample (N=149) reported treatment for ADHD. Of the 95 currently receiving treatment, 87 were taking a stimulant medication. The treated population demonstrated better attention and better employment outcomes than those who were not treated. Those who continued their treatment reported greater self-efficacy than those who did not. The researchers identify their sample population as a potential weakness because it was compiled from the national ADHD patient organization. The sample relies on self-reporting and may not be an adequate representation of the general population with ADHD. The findings indicate the tolerability and efficacy of stimulant medications into late-adulthood. In the future, large population based studies would be useful to create generalizable findings and treatment recommendations.

Chapter 3

Discussion and Synthesis

This review of literature has several applications for advanced practice. First, the use of stimulant medications is not associated with adverse cardiovascular side-effects or risk of sudden death. Despite the black box warnings, stimulant medications can be considered safe for use in children and adults. Therefore, practitioners should feel comfortable and confident prescribing them for their patients with ADHD. The findings regarding substance abuse indicate a need for practitioners to educate patients and parents about high risk behaviors and vulnerability in this population. Furthermore, they should be vigilant in their patient care and insure regular patient follow-up throughout the course of therapy for appropriate monitoring. Finally, practitioners need to be aware of their own attitudes regarding adult ADHD and recognize the long-term implications if it is left untreated. Practitioners should continue to educate themselves about treatment options, and should refer patients to specialists when needed.

Current research regarding cardiovascular safety includes many large population-based studies and long-term follow-up. Despite the strength of these studies, stimulant medications still carry a black box warning for sudden death. Providers and policy makers should consider current literature supporting the use of stimulant medications for ADHD, and avoid harboring concerns from the past. Further research may choose to focus on dose-related effects of stimulant medications to determine variability in cardiovascular response. Overall, research should continue to monitor long-term cardiac outcomes as the population of patients with adult ADHD continues to grow. The literature regarding substance abuse is clear in demonstrating increased risk throughout the lifetime, however it is limited because of the lack of control trials. Obviously substance abuse is not a phenomenon that can be tested in a lab. However, future studies should

determine which ADHD medications may have the greatest protective effects, and how age of onset of therapy affects future substance abuse. Both patients and providers would benefit from stronger evidence in this area. The evidence regarding adult ADHD is very limited by the current nature of data. Since it is a relatively new topic of interest, the majority of data is demographical and qualitative. However, the evidence presented here provides enough reason for providers to consider the importance of stimulant medication therapy in adulthood.

The global limitations of this summary are the specific focus on stimulant medications and their impact on ADHD. ADHD is a dynamic disorder and requires careful consideration on multiple levels by providers and patients alike. Treatment for ADHD has largely been aimed at symptom control, and the progression of symptoms throughout the lifetime is still a topic of some debate. There are studies to suggest that non-stimulant therapy may be more beneficial as patients transition from adolescence to adulthood. Because this literature review focuses exclusively on stimulant medication, the recommendations herein may be inappropriately one-sided.

In conclusion the results of this literature review demonstrate the cardiovascular safety of long-term use of stimulant medications. These findings coincide with over a decade of similar research demonstrating both efficacy and safety in children. Future research should focus exclusively on adult populations and how initiation of stimulant-therapy may impact existing comorbid conditions such as hypertension. The investigation of substance abuse should be continued to determine how stimulant medications for ADHD may reduce the lifelong impact of the disorder on substance abuse. Current and previous literature has established that the problem exists, now future research should seek to remedy it. The current literature regarding adult ADHD including quality of life and stimulant medications demonstrates without a doubt the

need for pharmacological treatment. There are no current guidelines for the treatment of ADHD diagnosed in adulthood, therefore many more studies are needed to determine the true incidence of adult ADHD as well as the most effective treatment regimens. Overall the long-term effects of stimulant medications for ADHD include benefits such as improved social, educational, and occupational outcomes. Serious adverse effects are rare and overall long-term use of stimulant medication is considered both safe and effective. Providers should feel equipped to use stimulant medications in patients of all ages to promote lifelong symptom management and control.

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Article Matrix

Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Agarwal, R., Goldenberg, M., Perry, R., & IsHak, W. W. (2012). The quality of life of adults with attention deficit hyperactivity disorder: a systematic review. Innovations in Clinical Neuroscience, 9(5-6), 10-21.	The purpose of this study is to determine: • which metrics are used to assess quality of life (QOL) in adult ADHD •What is the impact of adult ADHD on QOL? • What effects do ADHD treatments have on QOL	Systematic review of literature using multiple databases including PubMed and Medline. Specific focus on studies that examined QOL of adult patients with ADHD, especially those using validated tools to quantify QOL. Reviewed a combination of qual/quant studies with a preference for quantitative data collected using valid QOL scales. Level V	Sample size: 36 24 studies used established QOL measures to quantify the QOL in adults with ADHD.
	Variables, Measurements	Findings	Future Implications
	Independent variables: age, gender, stimulant medications, non-stimulant medications, type of scale used for evaluation of QOL. **Dependent variables**: Reported QOL based on the above independent variables as measured by unique scales. **QOL measures** 1)WHO-QOL brief version and SF-36. Self-rating of QOL based on four domains; physical, psychological, social, and environmental. Strong correlational value of level of	•Non-stimulant medications for ADHD (Amoxetine) do not decrease reported symptomology but do improve perceived QOL as rated by the patient. •Stimulant medications (Adderall) decrease symptomology and improved executive functioning and improved QOL based on established metrics. •Patients with ADHD report lower QOL and	It is understood that adults with ADHD experience decreased QOL secondary to their ADHD symptoms. Because QOL measures have been proven to be valid and reliable, they are an important tool for goal setting and outcome measuring during pharmacologic therapy. Further research in the form of head to head trials would be beneficial to determine QOL improvement among individual classes of ADHD medications to determine superiority.

	symptomology and QOL. 2)QLESQ-S Rating scale demonstrating poor QOL in adults with ADHD and improved QOL in those taking stimulant medications 3)AAQOL Specific for adult ADHD; 29 items, health-related QOL. 4)AIM-A Assesses both global and ADHD specific QOL using six domains. Sensitive enough to discriminate symptom severity and medication subtype (a=>0.83) All metrics were demonstrated to be valid and reliable by the researchers.	demonstrate increased incidence of anxiety, depression, and daytime sleepiness. Specifically, poor social functioning in men and poor emotional control in women. • Current metrics do not yet identify what leads to decreased QOL and decreased sense of wellbeing in ADHD. • QOL improved greatest in those receiving stimulant therapy, followed by non-stimulant therapy, and placebo.	
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Awudu, G. H., & Besag, F. C. (2014). Cardiovascular effects of methylphenidate, amphetamines and atomoxetine in the treatment of attention-deficit hyperactivity disorder: an update. *Drug Safety*, *37*(9), 661-676. doi:10.1007/s40264-014-0201-8	To provide an update on the available evidence for any effects of methylphenidate, dexamphetamine, and atomoxetine on heart rate, blood pressure, or sudden cardiac death. The reviewers published known information regarding the same topic in 2009, this publication is considered an update. 5 key concepts 1) Methylphenidate and heart rate and blood pressure 2) Atomoxetine and heart rate	Review of literature published since 2009 composed of articles from the PubMed/Medline, Embase, PsycINFO, the Wolters and Kluwer OVID database, and the SAGE journal database. Using terms ADHD, cardiovascular/cardiac, heart rate, blood pressure, or QTc. Specific drug names were also included in the Boolean search. 20 papers were originally chosen for meta-analysis however due to	A total of 41 articles were reviewed and referenced. 9 studies discussed effects of methylphenidate on HR and BP in children and adolescents 8 studies discussed effects of Atomoxetine on HR and BP in children and adolescents 7 studies discussed the effects of amphetamines on HR and BP in children and adolescents 5 studies discussed ECG changes with ADHD medications

	and blood pressure. 3) Amphetamines and heart rate and blood pressure 4) Electrocardiogram changes with ADHD medication 5) Sudden death and ADHD medication	lack of standardized measurements on among studies it was determined the literature would be synthesized using tables when appropriate. Level V	6 studies discussed sudden death and ADHD medication Not all of these studies discussed HR and BP as primary outcomes.
	Variables, Measurements	Findings	Future Implications
	Independent variables: age, gender, equipment used for monitoring HR and BP, equipment used for ECG monitoring, dose of ADHD medication, **Controls:** length of therapy at measurement intervals, normal BP readings for age based on established guidelines **Dependent**: HR, BP, and ECG changes as a result of duration of therapy. (not dose dependent)	**Methylphenidate** 5/9 studies demonstrated statistically significant increase in HR at 90 min from administration of methylphenidate with a mean of <6 bpm. From a long term perspective data points up to 6 months did not demonstrate a clinically significant change in HR or BP. One study did report a clinically significant increase in HR at 14 months followed by a clinically significant decrease at 3 and 8 years respectively. **Atomoxetine** No studies to determine immediate effects (within two hours of administration). No statistically significant changes in BP or HR up to 6 months. At 12 months a statistically significant increase	This update of the current literature demonstrates a significant gap in recent studies that investigate the cardiovascular safety of ADHD medications over the long-term. Less than 5 of the reviewed studies collected data >5 years. Long-term studies with specific interest in cardiovascular outcomes are needed to determine the overall safety of these medications. Beyond this data, this update does not demonstrate any new findings in regards to clinically significant ECG changes, changes in HR, BP, or risk of sudden death. Weaknesses of current studies are lack of allowance for age related changes in HR and BP which are considered normal. These measures should account for age progressions and

		in HR (+3.26+-14.32) was noted. Overall transient or marginal increases in BP and HR occurred but were not considered clinically relevant. **Amphetamines** Results limited by small number of studies since 2009, None of the studies examined cardiac outcomes as a primary endpoint. However, all studies reported a small <6 bpm increase in HR. No statistically significant changes in SBP or DBP were identified. However, attention was paid to outliers and further study revealed family history of CAD and MI in patients who present with elevated SBP. **ECG Changes** No clinical data supported ECG changes included prolonged QTI or arrhythmias in patients taking methylphenidate, amphetamines, or atomoxetine. May be limited by small sample size and lack of ECG changes as primary study outcome. **Sudden Death** As it relates to suicide, there is a known increased risk of suicide completion among patients with ADHD, no correlation has	measure changes from baseline with respect to these values. Dose dependent studies would also be useful to determine how immediate release versus extended release medications may affect HR and BP in the short and long terms.

		been identified between medication for ADHD and incidence of suicide; may be attributed to characteristic impulsivity. No studies demonstrated increased risk of sudden cardiac death in patients taking medication for ADHD as compared to the general population. Because of the relative low risk of sudden death in children and relatively increased risk of sudden death in adults, age parameters are an important distinction.	
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Barbaresi, W. J., Colligan, R. C., Weaver, A. L., Voigt, R. G., Killian, J. M., & Katusic, S. K. (2013). Mortality, ADHD, and psychosocial adversity in adults with childhood ADHD: a prospective study. *Pediatrics, 131*(4), 637-644.	The goal if this study is to provide information regarding the cumulative risk for adverse long-term outcomes associated with childhood ADHD. This study describes mortality risks into adulthood which have not been previously identified. Outcomes of interest: 1)Mortality secondary to suicide or accidents 2)Incarceration rate 3)Persistence of ADHD into adulthood and risk of comorbid psychiatric conditions	Prospective cohort study comprised of a population based sample determined from existing school and health facility records. This information was used to determine vital status and its correlation with diagnosis of ADHD and was compared to standardized mortality ratios for the same population (control group). For determination of incarceration, adult ADHD status and other psychiatric disorders mailings	Study participants were selected from a birth cohort (1/1/1976-12/21/1982) based on residence in Rochester, MI until >5 years of age and having previously granted permission to access medical records N=5718. Subjects were then determined to have ADHD based on these records N=367. The control group was established from the remaining subjects not including those with severe disability or who had denied further access to their

		and follow up phone calls were used combined with public websites with information regarding criminal convictions. A standardized neuropsychiatric interview was administered. Level IV	records. Of the 367 eligible ADHD subjects, 232 agreed to participate in the prospective study.
	Variables, Measurements	Findings	Future Implications
	Independent variables: gender, age, type of ADHD treatment during childhood, sociodemographic factors during childhood **Dependent variables:** mortality, incarceration rate, risk of comorbid conditions **Measurements** For determination of vitality, data was simply collected and the risk for specific outcomes mortality was determined by comparing the percentage prevalence of each outcome in the ADHD population versus the control. Mini international Neuropsychiatric interview (M.I.N.I.) with the adult module for ADHD was administered to all prospective study participants. Determination of adult ADHD was defined by the persistence of symptoms of inattention,	**Mortality** Cause related mortality for accidents was similar among controls and ADHD cases. Cause related mortality for suicide was significantly higher among ADHD cases than controls. Further investigation determined that of the 7 ADHD case related deaths, 5 had a documented history of substance abuse disorder and 1 other psychiatric comorbidity. **Incarceration** 2.7% of identified ADHD subjects were incarcerated at the time of this report, due to data collection limitations, rates of incarceration over the lifespan were not included. **Persistence of ADHD into adulthood and comorbid**	Significant associations between childhood ADHD and adult psychiatric conditions demonstrate a need for continued research to determine the effectiveness of ADHD therapy into adulthood and how it may moderate these risk factors. Further research is needed to determine the rate of incarceration as it relates to childhood ADHD. Overall mortality from suicide is still not completely understood and requires further research. Substance abuse is an of great clinical concern and should be assessed frequently in adolescent and adult ADHD patients.

	hyperactivity, and impulsivity with >4 symptoms being present.	**psychiatric disorders** Adults with ADHD were significantly more likely to have a comorbid psychiatric disorder than the control group (56.9 % versus 34.9%), The most common adult problems being alcohol abuse, antisocial personality disorder, other substance abuse, and generalized anxiety disorder. Total cases reporting both adult ADHD and comorbid psychiatric disorder N= 55, cases reporting adult ADHD only N= 13	
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Brod, M., Schmitt, E., Goodwin, M., Hodgkins, P., & Niebler, G. (2012). ADHD burden of illness in older adults: a life course perspective. *Quality of Life Research, 21*(5), 795-799 5p. doi:10.1007/s11136-011-9981-9	**Purpose** To explore the burden of illness and impact on the patients' quality of life experiences in older ADHD adults.	A qualitative pilot study to determine impact of ADHD symptoms on daily functioning, social, psychological, and physical well-being throughout the life course. Method Telephone interviews were conducted over 60-90 minutes using an interview guide to collect the following data; demographic background, employment status and history, diagnoses, ADHD medications and symptom history, experience with	Letters seeking referrals were sent to 188 psychologists. Inclusion criteria were ADHD diagnosis by health care professional, English speaking, and age >60. 27 patients were referred, 24 met criteria for completion. Mean age of sample was 66, mean age of ADHD diagnosis was 57. 68% of the sample were mean. 99% Caucasian.

		and perception of living with ADHD. The adult ADHD quality of life measure if a validated tool which was also completed by each respondent. Level VI	
	Variables, Measurements	Findings	Future Implications
	Independent Age, gender, race, adult onset ADHD, ADHD diagnosis by healthcare provider, English language. **Dependent** treatment history, primary symptoms and impairments, positive aspects of ADHD, and burden of ADHD across the life course Qualitative researchers conducted, recorded, and transcribed the interviews. Results were coded for analysis. The AAQoL was used to quantify QOL perceived by participants. Results were compared to the control for the AAQoL validation study.	**Treatment History** 50% of participants report seeking treatment after self-identifying ADHD symptoms. 100% of participants took medication for ADHD at some point and 22/24 reported benefits including improved focus, listening, and reading comprehension. 25% reported medication side effects; nausea, insomnia, headache, and anxiety **Primary Symptoms and Impairments** Inattention was reported by 71%, impulsivity 58%, hyperactivity 54%, and disorganization 54%. **Positive aspects of ADHD** 46% of participants believed ADHD made them more creative and able to hyper focus when interested in a topic. **Burden of ADHD** 63% of participants reported a tangible	This study supports the hypotheses that adult ADHD symptoms have a meaningful long-term effect on QOL in the form of career success, social relationships, and financial management. This small sample size and qualitative data cannot be generalized to larger populations, however as the rates of adult ADHD diagnosis increase, so will the population of older adults with ADHD. Future studies and current treatment measures should be aimed at minimizing these negative impacts across the lifespan.

		cumulative impact of their ADHD on their finances related to impulsivity and inability to manage debt. 71% stated their ADHD had alienated friends, family, and co-workers. **Assessment of ADHD on QOL** The mean age of the comparison group was 41, but the questionnaire demonstrated a significantly lower life productivity score in the older adult. However, the life outlook score was significantly better compared to the younger sample.	
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Chang, Z., Lichtenstein, P., Halldner, L., D'Onofrio, B., Serlachius, E., Fazel, S., & ... Larsson, H. (2014). Stimulant ADHD medication and risk for substance abuse. *Journal of Child Psychology And Psychiatry, And Allied Disciplines*, *55*(8), 878-885. doi:10.1111/jcpp.12164	The purpose of this study is to determine the effects of long-term use of ADHD medications as they relate to substance abuse. There is a known correlation between the diagnosis of ADHD and substance abuse, but inconclusive data about how medication for ADHD may contribute to substance abuse as well.	Population based longitudinal cohort study. Data were analyzed using cox regressions with standard errors. Specific controls were used to isolate the outcome of interest as it pertains to the general population and to avoid inappropriate skewing. The outcome of substance abuse for example was examined in patients based on covariates of civil employment, education, urban living, and family income. Previous	A Swedish population based sample of nation-based register of persons born from 1960-1998 with a diagnosis of ADHD based on the ICD 10 code F90 and known treatment via the prescription drug register. Substance abuse was identified using national patient cause of death and crime registries.

		substance abuse, criminal convictions (other than substance abuse) and other psychotropic medications were also taken into account.	
	Variables, Measurements	Findings	Future Implications
	Independent variables: Age, gender, age of ADHD diagnosis, type of ADHD medication, duration of treatment, and individual controls as previously described. **Dependent Variables:** incidence of substance abuse with respect to covariates. Hazard ratio for substance abuse Calculated using Cox regressions comparing medicated and non-medicated periods to quantify the risk of substance abuse with controls for various social/demographic variables.	Patients who were not taking ADHD medications in 2006 were compared to those taking medications in 2006 and data was recovered from 2009 to determine long-term effects and trends in substance abuse. Analysis were also done on the basis of sex and age. These analyses determined there was a 48* decrease in the substance abuse ratio HR= 0.52 95% confidence interval among patients who were medicated for their ADHD versus those who were not. Furthermore, after controlling for criminal convictions prior to 2006, previous substance abuse, and sociodemographic factors such as low income there was still a 31% decrease in substance abuse among medicated patients with ADHD.	This information should encourage community based providers to feel more comfortable when prescribing medications for ADHD. Despite popular opinion and black box warnings, this study did not demonstrate correlation or causation among ADHD medications and propensity for substance abuse. If anything ADHD medications can be protective against substance abuse in ADHD patients.

Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Groenman, A. P., Oosterlaan, J., Rommelse, N., Franke, B., Roeyers, H., Oades, R. D., & ... Faraone, S. V. (2013). Substance use disorders in adolescents with attention deficit hyperactivity disorder: a 4-year follow-up study. *Addiction*, *108*(8), 1503-1511 9p. doi:10.1111/add.12188	**Purpose** To examine the relationship between a childhood diagnosis of attention deficit hyperactivity disorder (ADHD) with or without oppositional defiant disorder (ODD)/conduct disorder (CD) and the development of later alcohol/drug use disorder [psychoactive substance use disorder (PSUD)] and nicotine dependence.	Prospective population based cohort 4-year follow up study. Subjects from IMAGE study age 5-17 years with one available sibling (not required to have ADHD diagnosis) Data collection was done via in person interviews at 1 of the three sites. Parent and teacher Connor's rating scales were part of baseline data to quantify ADHD symptoms Data were analyzed based on prevalence rates and hazard ratios compared to control. Level IV	Participants from the Belgian, Dutch, and German part of the International multicenter ADHD genetics (IMAGE) study. Age 5-17 years attending outpatient clinics, and one of their siblings, and control groups from the same geographic area. Mean age of re-assessment 16.4 years N= 1017 ADHD N=511 Unaffected sibling N=286 Healthy control N=220
	Variables, Measurements	Findings	Future Implications
	Independent variables Age, race, gender, diagnosis of ADHD, diagnosis of oppositional defiance disorder, diagnosis of conduct disorder **Dependent variables** substance use diagnosis, alcohol use, alcohol dependence, nicotine use, nicotine dependence, age of use Parental account of childhood symptoms (PACS) interview was conducted at baseline	The population of children with ADHD were 1.8 times more likely to develop psychoactive substance use disorder and 8.6 more likely to develop nicotine dependence than healthy controls. Unaffected siblings were not at increased risk for PSUD or nicotine dependence.	This large population based study demonstrated an increased risk of substance abuse and nicotine use in adolescents for children who are diagnosed with ADHD. These findings correlate with other published studies that demonstrate a positive correlation between ADHD and substance abuse. This study does not address treatments

	PACS and Connor's scales were used to supply operational definitions to characteristics associated with ADHD Alcohol user's identification test (AUDIT) Scores form 0-40 9 or greater indicated alcohol abuse And greater than 15 was alcohol dependence Drug abuse screening test (DAST) scores 0-20. Cutoff of 5 for possible drug use disorders Fagerstrom test for nicotine dependence (FTND) scored 0-10. Cutoff of 6 indicated nicotine dependence. Criteria may be met by individual or parent report data alone	ADHD and comorbid conduct disorder increased incidence of PSUD. ADHD and ODD did not increase risk compared to healthy control group. Participants with childhood ADHD diagnosis had younger age of first substance use and nicotine use compared to healthy controls. Unaffected siblings had a younger onset of nicotine use compared to healthy controls.	for ADHD to determine if patients were or were not on therapy at the time of diagnosis or the time of follow-up. Knowing whether or not patients who exhibited substance abuse disorders were treated for their ADHD is very important for future practice.
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Habel, L., Cooper, W., Sox, C., Chan, K., Fireman, B., Arbogast, P., & ... Ray, W. (2011). ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA: Journal Of The American Medical Association*, *306*(24), 2673-2683 11p.	**Purpose** To examine whether current use of medications prescribed primarily to treat ADHD is associated with increased risk of serious cardiovascular events in young and middle-aged adults.	Large retrospective, population-based cohort study utilizing chart review from four different facilities. Beginning in 1986 and ending in 2005. Level IV	adults aged 25 through 64 years with dispensed prescriptions for methylphenidate, amphetamine, or atomoxetine at baseline and 2:1 controls chosen to match cases for site, birth year and sex. N=443,198
	Variables, Measurements	Findings	Future Implications
	Independent variables age, sex, data site, calendar year at cohort entry, duration of	In all groups including current users, remote users, and non-users there were no indications	Because data was collected using prescription database and insurance database

	therapy, type of ADHD medication **Dependent variables** MI Sudden cardiac death Stroke Other serious cardiovascular event Cardiovascular risk score (CRS) was created to allow for cofounders that would affect the endpoints but are not related to medication for ADHD I.e. use of psychotropic medications, diabetes mellitus, obesity, smoking-related and health care utilization Multi-variate logistic regression was used to account for other non-controlled confounders such as family history of CVD, substance abuse, and ethnicity.	that risk rations were increased for any of the endpoints of interest. Once the results were mitigated using the CRS and analysis of race, etc. There were still no statistically significant indicators that ADHD mediation use part or present resulted in increased incidence of serious cardiovascular events.	information it does not necessarily reflect results of medication compliance, since medications may have been prescribed and not taken. Because of the large sample size, it is reasonable to assume that these findings can be generalized to general practice. Higher levels of evidence using controlled trials are difficult because of the length required for the observation of study outcomes.
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Hammerness, P. G., Surman, C. H., & Chilton, A. (2011). Adult attention-deficit/hyperactivity disorder treatment and cardiovascular implications. *Current Psychiatry Reports*, *13*(5), 357-363. doi:10.1007/s11920-011-0213	To provide an update on currently approved medications for ADHD with focus on cardiovascular risk factors associated with sympathomimetic mechanisms of action.	Review of literature from 2009 to 2011 based on PubMed database search. Search limiters: adult, clinical trials, English language. Also including guidelines published by the AAP and AHA. Level II	A total of 50 articles were listed in the review of literature, the majority of the implications in the article were demonstrated from 4 large sample size studies N= 226,420,359, and 133 respectively. With a preference for long term data points including one study with data collected over 24 months.
	Variables, Measurements	Findings	Future Implications
	Variables of interest in each study were HR, resting and active, systolic and diastolic	**Stimulant class medications** Trends in RCT demonstrated an increase in HR (4-	Stimulant medications are still considered most effective therapy in adults and are

	blood pressure, and ECG changes. Independent variables were age, gender, type of medication, medications dose, and age of diagnosis. Information was not given regarding how the measurements were recorded, rather the authors summarized the findings of each study and how they were significant to practice.	10) BPM, increase in BP (1-5 mmHg) in healthy pre-screened Adults. These markers vary throughout duration of therapy. As many as 60% of patients report subjective symptoms such as headache, dry mouth, drowsiness, and insomnia. Occurrence of subjective symptoms did not correlate with incidence of tachycardia or HTN. **Non-stimulant Medications** Based on measure of effect size, non-stimulants are inferior to stimulants in regards to efficacy. RCT demonstrates mean elevations of 5 BPM and 2 mmHg for HR and BP. Amoxetine is also associated with increased subjective reports of palpitations, but fever reports of HA, and insomnia. No EKG changes were associated with stimulant or non-stimulant therapies.	considered safe as supported by clinical date up to two years. Beyond that, further long-term studies are needed to determine cardiac adverse effects. Based on the literature for Amoxetine, it is considered second line therapy unless the patient 1) cannot tolerate stimulant secondary to insomnia or weight loss or 2) the patient has history of substance abuse. Also, secondary to its mechanism of action, Amoxetine shows greater emotional control and positive outcomes for women. This data is useful for prescribers.
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Huang, Y., & Tsai, M. (2011). Long-term outcomes with medications for attention-deficit hyperactivity disorder: current status of knowledge. *CNS Drugs, 25*(7), 539-554.	Determine long term outcomes of medications for ADHD, overview of currently available data regarding stimulants and non-	Systematic review of literature. Specifically, open-label longitudinal case-control or randomized controlled trials of	Data retrieved using PubMed database with keywords long-term outcomes of ADHD medications. All studies were published since

doi:10.2165/11589380-000000000-00000	stimulants. Highlight areas for further research.	at least 6 months duration. Level III	2001. A total of 128 articles were reviewed.
	Variables, Measurements	Findings	Future Implications
	Independent variables Age, sex, dose of medication, stimulant versus non stimulant medication, age of diagnosis **Dependent Variables** Effectiveness, adverse effects (subjective), growth effects, cardiovascular effects, Tics and Tourette's syndrome, substance abuse, quality of life, academic achievements in high school. Long term outcomes > 5 years in children and long term outcomes in adulthood were describes separately regarding safety, efficacy, and tolerability.	**Effectiveness** Medication therapy including stimulant and non-stimulant options was superior to behavioral cognitive therapy in effectiveness of symptom reduction. Both Amoxetine and stimulant therapy demonstrated long-term clinical improvement from a period of 14-24 months. At 36 months of therapy, the advantages were less apparent. This may be attributed to age related changes in ADHD severity, or changes in intensity or adherence to therapy. **Adverse Effects** RCT evaluating stimulant medications over five years demonstrated persistence of headache, appetite loss, and abdominal pain to the final endpoint, however none of the participants discontinued the therapy due to these adverse effects, suggesting tolerability. Severity of reported side	Stimulant and non-stimulant medications are effective for treating ADHD throughout the lifespan regardless of age of diagnosis, more longitudinal studies are needed to determine specific safety and efficacy considerations. Stimulants are still considered first line in children and adults, however evidence suggests that in adulthood and in the presence of other comorbid psychiatric conditions Amoxetine may have greater impact on QOL of symptom reduction. Known adverse effects of stimulant medications appear to persist in long-term therapy but are considered tolerable. Cardiovascular effects including increased HR and BP are small but further data is needed to determine the long-term risks. Medication for ADHD does not contribute to later substance abuse, and early initiation of therapy may have protective influences by limiting

		effects varied among type of stimulant medications suggesting they could be managed by changing drug therapies. **Growth Effects** Similar to previous reports, the literature shows a delay in progression of height and weight at 12 and 15 months of therapy which were recovered by 24-36 months. This is true of stimulant and non-stimulant therapies. **Cardiovascular Effects** For Amoxetine and stimulant medications, small but statistically significant increases in BP were noted. Stimulant therapy also resulted in statistically significant increases in HR. Despite these changes, No EKG changes were noted, leading authors and researchers to determine the cardiovascular effects are manageable. Further research is needed to determine the long-term implications of these changes. Therapy remains contraindicated for patients with history of cardiac	impulsive and antisocial behaviors.

		abnormalities, syncope, angina, or family history of sudden cardiac death. **Tics and Tourette's** No evidence to suggest that stimulants increase the incidence of or exacerbate tics or Tourette's. **Substance Abuse** Stimulants administered in childhood do not increase the risk of later substance abuse. One study demonstrated a positive relationship between age of treatment initiation and non-alcoholic substance abuse. **Quality of Life** Most data focuses on treatment with Amoxetine, as a generalization, studies demonstrate improved QOL in patients receiving treatment for ADHD compared to those who do not. **Academic Achievements** Patient's receiving at least 1 year of stimulant therapy scored higher in all academic areas than those not being treated for their ADHD.	
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Kelly, A. S., Rudser, K. D., Dengel, D. R., Kaufman, C. L., Reiff, M. I., Norris, A. L., ... & Steinberger, J. (2014). Cardiac autonomic	**Purpose** To compare markers of cardiovascular health in youth	Cross-sectional observational study of children with ADHD taking	N=138 children and adolescents 85 with ADHD and 53 control participants

dysfunction and arterial stiffness among children and adolescents with attention deficit hyperactivity disorder treated with stimulants. *The Journal of pediatrics*, *165*(4), 755-759	diagnosed with ADHD by the use of stimulant medication with healthy controls.	stimulant medications with a control group comparison. Data was collected by trained study staff and was standardized by direct observation of medication administration, and standards of measure for heaight weight, HR, and BP. SphyhmoCor MM3 systems measured HR variability and magnitude of pulse wave velocity to determine arterial stiffening. Level IV	from an outpatient pediatric clinic. ADHD patients must be taking stimulant medication either Adderall or methylphenidate derivative. Exclusion criteria were known cardiovascular disease. Mean cumulative stimulant treatment for the group was approx. 3 years.
	Variables, Measurements	Findings	Future Implications
	Independent Age, gender, height, weight, BMI, length of therapy, Tanner stage of development, caffeine consumption by participants, time engaging in vigorous exercise for the past 14 days (28% in control and ADHD groups) **Dependent** Blood pressure, heart rate, heart rate variability, carotid-radial pulse wave velocity, carotid artery augmentation index, radial artery augmentation index, brachial artery flow-mediated dilation, and digital reactive hyperemic index. Indices were measures using the sphygmoCor MM3 system and standard ultrasound	Mean age and Tanner stage distribution were similar among groups. ADHD group demonstrated lower mean BMI than control group. ADHD group had greater resting SBP (3.9 mm Hg), greater resting HR (+9.2 BPM), carotid artery augmentation index (AIx) (7.2%), and pulse wave velocity (0.36 m/s). No statistically significant differences in the groups for radial augmentation index. These results demonstrate increased HR variability and arterial stiffening in	Because the control group in this study was comprised of healthy children without ADHD it is impossible to say if the increased variability in HR and arterial stiffness is related to the stimulant medication or is attributed to the underlying pathology of ADHD itself. A further longitudinal study with participants who have ADHD but are not receiving stimulant medications would be needed to determine causation. Because this study evaluates these effects in the acute setting, further

	Measures were taken at intervals up to 90 minutes after medication ingestion. Statistical analysis was performed using t-test for covariates and robust variance estimation was used for Cis and P values.	the population of patients with ADHD. Based on the data analysis, elevation in HR and BP were casual but not directly correlated to HR variability and arterial stiffness. These findings indicate greater sympathetic activation resulting in more extreme values in children with ADHD than have previously been observed in children with type I DM or childhood obesity, which are known cardiovascular risk factors. There was no statistically significant difference among results in patients based on duration of therapy or dose of stimulant medication.	research is needed to determine how they persist over time. Because HR variability and arterial stiffness are known independent risk factors of cardiovascular disease it is important to determine if these effects are in fact caused by the use of stimulant medications and if persist through long-term therapy. These measures are more indicative of cardiovascular risk than HR and SBP measurements alone and should be used as standard measures in future studies.
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Klein, R. G., Mannuzza, S., Olazagasti, M. R., Roizen, E., Hutchison, J. A., Lashua, E. C., & Castellanos, F. X. (2012). Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Archives Of General Psychiatry*, *69*(12), 1295-1303. doi:10.1001/archgenpsychiatry.2012.271	**Purpose** To determine functional outcomes of childhood ADHD into the fourth and fifth decades of life (span 33 years). **Outcome Questions** Occupational Economic Educational attainment Marital history Lifetime psychiatric disorders Incarcerations	Prospective 33-year follow-up study with masked clinical assessments. Follow up interviews conducted at 18 years of age, 25 years of age, and 41 years of age. At 41 years of age the final interviews were conducted by trained and	The original sample was obtained by teachers referring white males age 6-12 from years 1970-1978. Boys were included if their referral criteria were impulsivity and hyperactivity without aggression, history of antisocial behavioral problems, and whose IQ was >85. The control group was selected

		supervised doctoral level clinical psychology candidates masked to all antecedent data. Telephone and personal interviews were conducted. Level IV	form white males of the same age who had existing medical records at the same medical record and were seen for minor acute conditions or routine medical care without documentation of behavioral problems. N= 135 men with childhood ADHD and 136 without.
	Variables, Measurements	Findings	Future Implications
	Independent variables Age, male gender, ADHD diagnosis based on behavioral documentation consistent with DSM-IV criteria, absence of antisocial or neurologic disorder, education and training of interviewers. **Dependent variables** Reported social and functional outcomes. Education as determined by years of education and highest degree obtained. Occupational based on current employment status, job satisfaction, work relationships, lateness, job changes, and firings. These items were rated by interviewers on an anchored scale from 1-6. (1) Superior (6) Poor Social function by inquiring about friendship, social and leisure activities, also rated on a 6-point scale. Incarceration (reform school or jail time of	On average participants with ADHD had 2.5 fewer years of school than controls as well as fewer high-level degrees. ADHD participants demonstrated lower occupational attainment levels (4.7 versus 3.0). Lower educational and occupation understandably resulted in lower socioeconomic status. The average salaries of the effected population versus the control differed by $40,000. Patients with ADHD demonstrated 3-fold greater rate of non-alcohol substance abuse and nicotine dependence. There was no significant difference in occurrence of anti-social personality disorders, anxiety, or mood disorders.	Weaknesses requiring further study; study was limited to white male participants, excluding date for women or other races. No documentation of ADHD treatment in childhood or adulthood was provided so the augmentation of these lifelong risk-factors by proper clinical identification and treatment cannot be postulated. This study is valuable because it evaluates the long-term functional outcomes associated with the diagnosis of ADHD itself. However, further studies with diverse sample sizes and greater information about treatment methods and influences would be needed for this information to be considered generalizable and

	more than one day) rated as positive or negative. Marital history as currently married or not, and history of divorce. Lifetime psychiatric disorders including anti-social personality disorder and substance abuse based on interviewer's data collection and hospitalization in a psychiatric facility. Lifetime prevalence of ADHD symptoms was assessed based on participants reported experiences and interviewer's assessment consistent with DSM-IV criteria.	Patients with ADHD had higher rates on incarceration and divorce than the control Interviewer reports of adult ADHD symptomology based on DSM-IV criteria were significantly less than subjective perceived ongoing effects of adult ADHD.	valuable to clinical practice.
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Lensing, M. B., Zeiner, P., Sandvik, L., & Opjordsmoen, S. (2015). Psychopharmacological treatment of ADHD in adults aged 50+: an empirical study. *Journal Of Attention Disorders*, *19*(5), 380-389 10p. doi:10.1177/1087054714527342	**Purpose** To study pharmacotherapy in adults age 50 or older with ADHD **Study Questions** 1) How well do stimulant medications work for this group of adults, many who have lived their whole lives undiagnosed and untreated? 2) Can adults age 50+ tolerate pharmacotherapy?	An Empirical study of use and persistence of psychopharmacological treatment for ADHD in older populations and to explore the association between treatment, symptoms, and life satisfaction. Anonymous survey of self-identified ADHD patients from a national ADHD patient organization. Likert scales allowed for quantitative data analysis using chi squared tests among categorical data, binary logistic regression analysis	The survey was mailed to 251 subjects who met inclusion criteria; diagnosis of ADHD by clinical specialist, and age >50. 166 returned the survey. 17 were excluded because either ADHD or age could not be confirmed N= 149 59.7% female Mean age of participants 55.8 Mean age of diagnosis 50.3

		was used to identify associations between characteristics and symptom severity. Level VI	
	Variables, Measurements	Findings	Future Implications
	Independent variables Age, Adult diagnosis of ADHD, gender, current or former treatment for ADHD, duration of treatment. **Dependent variables** Treatment impact on core symptoms of hyperactivity and inattention. Satisfaction of life, current health status, self-efficacy/ ADHD self-report scale (ASRS) four items of inattention and two items of hyperactivity/impulsivity. Frequency rated on a 5 point Likert scale 0 (never)- 4(very often). Clinical cutoff was 14 Health status assessed using Euroqol visual analogue scale (EQ-VAS) values from 0-100) 0 Being worst and 100 being best. Self-efficacy measured using the statement "IM able to manage daily demands well". 5 point Likert response from strongly disagree to strongly agree.	Characteristics of the study sample were classified based on three groups; currently treated with medication, stopped treatment with medication, and never treated with medication for ADHD. 87.9% had been treated using pharmacotherapy, 95 of which were currently still being treated. Those who were currently being treated with medication reported better attention than the non-medicated groups. Participants who had never been treated for ADHD reported worse current health status than the other two groups. Self-efficacy was higher in groups still being treated for ADHD compared to those who had stopped treatment. The three groups did not differ	Adults who were treated for their ADHD demonstrated increased attention and greater self-efficacy than those that were not treated. There were no significant differences in hyperactivity/impulsivity or overall favorable outcomes (I.E. clinically insignificant experience of ADHD symptoms) among treated and non-treated groups. Further research is needed to determine how age related progression of ADHD and age related variations in neurotransmitter activity may influence efficacy of stimulant pharmacotherapy in older adults.

		statistically significantly between favorable outcomes (ASRS <14). The majority of patients receiving pharmacotherapy for ADHD received methylphenidate.	
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Mahon, A. D., Woodruff, M. E., Horn, M. P., Marjerrison, A. D., & Cole, A. S. (2012). Effect of stimulant medication use by children with ADHD on heart rate and perceived exertion. *Adapted Physical Activity Quarterly: APAQ*, *29*(2), 151-160.	**Purpose** To examine the rating of perceived physical exertion-heart rate relationship during a graded exercise test performed to peak exertion in children with ADHD presently using stimulant medications compared with similarly aged children without ADHD.	Cross-sectional case control study. HR and RPE to be measured in study and control population during a standardized graded exercise test. Standardized RPE scale was used. Children were taught how to use the scale and then had a post-test evaluation for understanding. Exercise was done on an electronically-braked cycle ergometer; HR was measured using Polar monitors. Measures of peak HR and power output were recorded with the RPE. Data were plotted and analyzed by slope and intercept. Means and SD were determined for each group. Level IV	Participants volunteered for study and participants and parents consented to procedures. N=45, 20 children with ADHD and receiving stimulant medications (18 boys, 2 girls), 25 children without ADHD (12 boys, 13 girls).
	Variables, Measurements	Findings	Future Implications
	Independent variables	There were no significant differences in	Because current studies are being done to determine

	Age, stature, mass, type of medication, daily medication dose, equipment used for measuring HR and power output. RPE rating scale- values from 1-10 based on level of exertion **Dependent variable** Heart rate; resting and during maximum output, power output, and RPE measurement. Peak HR was taken as the highest two consecutive averages recorded during the test. Peak power output measured in W was prorated by duration of highest achieved test stage. Physical characteristics and peak exercise response were compared between groups using independent t-test.	physical characteristics among either group. Peak HR for both groups= 200 Power output (W/Kg) = 3.1 in the ADHD group and 2.8 in the control group. Mean RPE for both groups 9.8. The relationship of HR to RPE was determined by plotting slope and intercept. For the participants with ADHD mean intercept (bpm) were 132.4 whereas the mean intercept for the control group was 120.6. The slope (bpm/RPE) for the ADHD group was 7.3, and 8.1 in the control group. For children with ADHD taking stimulant medications at a given HR RPE will be lower and at a given RPE HR will be higher when compared to control. This could be due to an elevated resting HR. The greatest effect was demonstrated at lower intensities, and the effect began to level off as maximum HR was achieved.	the benefits of exercise therapy for children with ADHD it is important to note the differences in perceived exertion and heart rate. It is unknown if children adapt to the higher resting heart rate over time or how titrating medication dosages effect perceived exertion and HR. It is however important for clinicians to note that exertional efforts of children being treated with stimulant medications may not be accurately reflected by their subjective experiences of exertion.
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Martinez-Raga, J., Knecht, C., Szerman, N., & Martinez, M. I. (2013). Risk of serious cardiovascular	**Purpose** To comprehensively and critically review	Comprehensive search of relative databases	81 documents were included for the review based on

problems with medications for attention-deficit hyperactivity disorder. *CNS Drugs*, *27*(1), 15-30. doi:10.1007/s40263-012-0019-9	published evidence on association of medications for ADHD and risk of serious cardiovascular problems including QT/QTc prolongation and risk of sudden death in children, adolescents, and adults	(PubMed, EMBASE, and PsychINFO) for peer-reviewed publications up until July 21, 2012. Key terms: ADHD, amphetamine, Amoxetine, clonidine, guanfacine, methylphenidate, arrhythmia, cardiac, QT, sudden death and torsade's de pointes. Level II	discussion of cardiac related events specifically QT and sudden death, not excluded based on age, population, date of publication, or design type.
	Variables, Measurements	Findings	Future Implications
	Independent variables Age, gender, type of medication, dose of medication, duration of therapy. **Dependent variables** Heart rate, Blood pressure, ECG changes specifically QT prolongation and arrhythmia, sudden death.	**Amphetamines, Methylphenidate, and Amoxetine** All were associated with small increases in HR (3-6) bpm and elevation in systolic BP (2.1 mmHG) of these, the majority of studies indicated the elevations were not statistically significant in children and adolescents. In the adult studies, the increased HR became statistically significant and remained so at endpoints up to 3 years. No reports of QT/QTc prolongation in any studies. **Arrhythmias** Arrhythmias were reported in 3 cases associated with use of	Based on the comprehensive review of literature regarding cardiovascular side effects for ADHD medications it is evident that both stimulant and non-stimulant medications cause marginal elevations in HR and BP. These effects are sometimes transient in children and tend to be more persistent in adults. Regardless of their incidence, the literature does not currently support a relationship between these increases in HR and BP and overall cardiovascular risk.

		methylphenidate. One was immediately after IV administration, and one was after oral administration to a geriatric patient. The third case was in a healthy adolescent who used methylphenidate in conjunction with alcohol and nicotine. No arrhythmias were reported in the other drug classes. **Sudden Death** Of all the studies, incidences of sudden death were very rare and associated with concurrent use of other substances including alcohol, nicotine, and other stimulants. All of the studies concluded that ADHD medications are not associated with increased risk of sudden death, however patients should be screened for cardiovascular conditions prior to initiation of therapy.	
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Martinson, J., & Tang, H. (2010). Correlating family nurse practitioners' perspectives of adult ADD/ADHD with employed pharmacotherapy: a pilot study. *Journal of The American Academy of Nurse Practitioners, 22*(8), 424-430 7p. doi:10.1111/j.1745-7599.2010. 00527.x	**Purpose** To determine how family nurse practitioners in the state of Washington view adult ADHD and how these views affect the pharmacotherapy they employ.	**Design** Descriptive quantitative study; convenience sample **Methods** 30 question survey mailed anonymously to 126 participants.	Convenience sample based on current FNP practice in the state of Washington in the area of acute and primary care for adults and family, geriatric health care, adult and women's care, family and occupational health.

		Responses analyzed using descriptive and Kendall's rank correlations coefficient statistical methods. Level VI	Of the 126 mailed, 42 were returned completed response rate 41.6%, respondents were primarily female and Caucasian. Average practice length was 6-10 years seeing an average of 40-79 patients per week
	Variables, Measurements	Findings	Future Implications
	The questionnaire was developed to take 20-30 minutes to complete and focuses on two dimensions 1) personal views od ADD/ADHD and the awareness that personal values may impact the treatment provided 2) preferred pharmacotherapy for ADD/ADHD and the comfort level in diagnosis, treating, as well as providing patient education and making referrals for ADD/ADHD. 7 Items collected demographic data 16 of the items were statement assessed using a 5 point Likert scale including agreed, disagreed, and undecided Short open-ended questions were also used to invite qualitative data	Responses demonstrated a significant negative correlation between being comfortable diagnosing ADHD in adults and thinking it is important to refer to a specialist for treatment. There is a positive correlation between how respondent's views determine the treatments they use and their comfort level treating adult ADHD in general Results demonstrated majority of providers did not view patients with ADHD as lazy or likely to abuse their ADHD medications (90.2%, 82.9% respectively) 59% agreed adult ADHD is a disabling illness requiring treatment however 61% did not feel there was enough time for screening and diagnosis during a regular scheduled visit.	Despite established adult ADHD treatment guidelines, the majority of providers in this study felt comfortable diagnosing, managing, and discussing ADHD with their adult patients. The results demonstrated that provider attitudes towards adults ADHD do influence prescribing practices. However, it appears provider attitudes support the need for pharmacological and primarily stimulant management of the condition. This small convenience sample gives insight to the phenomenon of adult ADHD management but larger case control studies would be required to demonstrate relationships among provider beliefs and prescribing practices.

		In the qualitative portion, many providers indicated a preference to refer to specialist for diagnosis, and comfort in managing established medication regimens. 66.7% prescribed stimulant therapy for adult ADHD	
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
McCarthy, S., Cranswick, N., Potts, L., Taylor, E., & Wong, I. K. (2009). Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: a retrospective cohort study of children, adolescents and young adults using the general practice research database. *Drug Safety*, *32*(11), 1089-1096. doi:10.2165/11317630-000000000-	**Study aim** To identify cases of sudden death in patients prescribed stimulant medications and Amoxetine to determine association between these and sudden death.	A retrospective cohort study of children adolescents and adults taking medication for ADHD. Data was obtained from the UK General Practice Research Database via chart review and outcomes investigation using a questionnaire sent to PCPs. Patients were followed from date of first prescription to date of death, transfer out, age >21 years, or the end of the study. Level IV	Patients identified from the database were aged 2-21 years from January 1, 1993 to June 30, 2006 with a prescription for methylphenidate, dexamphetamine, or amoxetine. Of 18,637 patient years, 7 patients died. Cause of death was obtained for 6 patients.
	Variables, Measurements	Findings	Future Implications
	Independent variables Age, sex, type of medication prescribed. **Dependent variables** Incidence of sudden death Cause of sudden death Sudden death according to the	Of the 7 patients, 6 causes of death were known; overdose of unknown intent, stab wounds, pancreatitis, suicide, suicide, brain tumor.	This large population based study did not demonstrate any relationship among ADHD medications stimulant or non and an increased risk for sudden death. Based on the demonstrated rarity

	WHO- instantaneous death and all deaths occurring within 24 hours of an acute collapse, not including homicide, suicide, drowning, poisoning, or other unnatural causes. Standardized mortality ratios (SMR) were obtained using population data from the United Kingdom office for national statistics. The sample population was compared to the SMR using incident rate ratios.	None of the deaths met criteria for sudden death. All 7 of the patients who died were taking stimulant medications. Incidentally, the incident rate of suicide was much higher in this cohort than the general population based on SMRs.	of these events it may take a larger sample size to have the power to demonstrate the rate of occurrence. Incidental findings of higher risk of suicide among patients taking ADHD medications are a topic of current study and providers should be aware of these risks when treating this population.
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Nelson, A., & Galon, P. (2012). Exploring the relationship among ADHD, stimulants, and substance abuse. *Journal of Child & Adolescent Psychiatric Nursing, 25*(3), 113-118 6p. doi:10.1111/j.1744-6171.2012.00322.x	**Purpose** To explore current state of prescription stimulant use for ADHD and the possible link to substance abuse.	Current literature review accessed from PubMed database and cumulated index of nursing and allied health literature. Gather empirical data regarding the topic; identify what is known. Level V	English language articles discussing ADHD, stimulant medications, and substance abuse. N= 34 articles
	Variables, Measurements	Findings	Future Implications
	Phenomenon of interest Gender, culture, ADHD as diagnosed by healthcare professional, age, socioeconomic status **Outcomes** Substance abuse Substance abuse- the inappropriate use of prescription or non-prescription drugs, alcohol, or other agents	Boys are 2.3 more likely to have ADHD than girls. Girls are more likely to present with inattentive type; boys are likely to present with hyperactive type. Cultural influences affect perceived severity of ADHD behaviors. Majority of ADHD assessments are	The current literature demonstrates carried and conflicting reports regarding the risk of substance abuse in patients with ADHD. The majority of data indicate that early treatment of ADHD leads to more positive social functioning outcomes and may have a protective

	DSM-IV definition of substance abuse- a maladaptive pattern of substance use leading to clinically significant impairment	self-report measures with little consensus among providers. Current research demonstrates patients with known substance abuse disorder have a higher prevalence of ADHD compared to the general population The hallmark findings of impulsivity cannot be excluded as a predisposing character trait for substance abuse. No clear link between stimulant use and substance abuse has been made, independent of age of medication initiation.	effect against substance abuse. ADHD occurs more frequently in the population of patients with known substance abuse disorders and should be a consideration for clinicians involved with these special populations. Further longitudinal controlled studies are needed to make delineate cause and effect relationships among ADHD diagnosis and substance abuse outcomes.
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Pitts, M., Mangle, L., & Asherson, P. (2015). Impairments, diagnosis and treatments associated with attention-deficit/hyperactivity disorder (ADHD) in UK adults: Results from the lifetime impairment survey. *Archives of Psychiatric Nursing*, *29*(1), 56-63 8p. doi:10.1016/j.apnu.2014.10.001	**Purpose** To assess the degree to which ADHD impairs patient's everyday lives, and identify areas of life most impaired by this condition.	Large online-based opinion survey. The survey was designed by psychiatrists and psychologists specializing in ADHD. Questions about impairment were combined into 10 scales evaluating the level of difficulties currently encountered by patients with ADHD versus a control. Adults with and without ADHD were compared using t-tests for continuous data	The sample population came from a voluntary consumer database for market research. Participants were identified by their answer to demographic questions including whether a doctor or healthcare professional has ever made a diagnosis of ADHD. A total of 210 participants were included in the affected and control groups. (105 each).

		and chi squared tests for categorical data. Mean impairment and symptom scores were calculated based on aforementioned scales. Level VI	
	Variables, Measurements	Findings	Future Implications
	Independent variable Adult age, diagnosis of ADHD by a medical professional. **Dependent variable** ADHD impairment and symptom scores Impairment and symptom scale subjects • Mood/temper control • Work impairment • Self-organization and planning • Involvement • Social impairment • Partnership impairment • Financial impairment • Rule-breaking behavior • Perceived impact • Perceived impairment	Based on the impairment and symptom scales there were significant differences among the ADHD and control groups in 7 areas; mood/temper, work impairment, self-organization. Social impairment, partnership impairment, financial impairment, and rule-breaking behavior ($P<0.001$). Demographic data demonstrated a broad range of co-occurring conditions, especially sleep problems, and anxiety. 1/3 of adults with ADHD received no treatment for their condition despite diagnosis by a medical professional.	The individual items on each of the scales provide great insight into the specific obstacles faced by adults with ADHD. Long-term, patients with ADHD experience greater difficulty in all aspects of life including educational, work impairment, and social functioning. Despite demonstrated and reported impairments, not all patients received treatment for their condition. Only 25.8% reported treatment with medication. This study did not examine relationship between treatments and severity of impairments to determine therapeutic benefits. This study highlights the need for further larger population based studies to determine interventions which may augment patient's perception of ADHD impact

			and impairment over time.
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Winters, K. C., Lee, S., Botzet, A., Fahnhorst, T., Realmuto, G. M., & August, G. J. (2011). A Prospective Examination of the Association of Stimulant Medication History and Drug Use Outcomes among Community Samples of ADHD Youths. *Journal Of Child & Adolescent Substance Abuse*, *20*(4), 314-329 16p. doi:10.1080/1067828X.2011.598834	**Purpose** To describe the relationship of psychostimulant medication during childhood and subsequent substance use disorders and tobacco use.	Longitudinal follow up study of an epidemiologically derived community based sample diagnoses with ADHD during childhood. DSM-IV substance use criteria have been assessed at the three most recent data points. Data collected using in person and telephone interviews, collectors were not blind to ADHD status. Data was analyzed using the GEE method and was controlled for age and gender. Level III	This sample was obtained from a larger ongoing study of youths identified to have disruptive behaviors before the age of 7. Patients in this sample have already been assessed at multiple data points at 11-15, and 12-16 years of age. ADHD sample N=149 and control N=93.
	Variables, Measurements	Findings	Future Implications
	Independent variables Age, age of diagnosis, diagnosis with DSM-IV criteria for ADHD, externalizing versus non externalizing ADHD. Socioeconomic status, and medication history were accounted for. **Dependent variables** Prevalence of alcohol use disorder, prevalence of substance use disorder, prevalence of nicotine use Socioeconomic status determined using four	Difference in frequency of substance use was only statistically significant at T4 for marijuana use among ADHD participants. There was no difference in outcomes among the three different medication groups. The overall incidence of substance abuse and nicotine use is higher in the ADHD population	This study did not randomize its subjects to be able to determine experimentally if medication for ADHD with controls for age may actually decrease rates of substance abuse. The study does negate the previously published notion that stimulant medications increase the rate of substance abuse later in life. Further experimental studies would be

	factor index of social status based on parental reporting ranged from unskilled to major business/professional. Medication history was determined by simple reporting of psychostimulant medication use 1) never used, 2) medication prescribed and used up to age 12, but no later, 3) medication prescribed and used after age 12 including childhood and later Substance use was measured using DSM-IV criteria for substance use disorders module of structured interviews.	than in the normal control group. There is no evidence to suggest that ADHD medication at any time period increases risks of substance abuse later in life.	needed to determine how ADHD medications may be beneficial in reducing the lifetime instance of substance abuse in this population.
Author, Date	Topic, Purpose, Study Questions	Method, Study Design	Sample, Population
Winterstein, A. G., Gerhard, T., Kubilis, P., Saidi, A., Linden, S., Crystal, S., & ... Olfson, M. (2012). Cardiovascular safety of central nervous system stimulants in children and adolescents: population based cohort study. *BMJ: British Medical Journal (Clinical Research Edition), 345*e4627-e4627 1p. doi:10.1136/bmj.e4627	**Objectives** To evaluate cardiac safety of central nervous system stimulants in children and adolescents.	Population based retrospective cohort study Utilized automatic claims data for Medicaid participants from years 1999-2006. Data included inpatient and outpatient services as well as medications reimbursed by Medicaid. Death records were obtained from social security master death file and the national death index. Data were analyzed using time survival analysis framework to compare data endpoints	Sample assembled of children and young people (age 3-18) from 28 Medicaid programs with a diagnosis of ADHD separated into two groups based on stimulant use or non. Exclusion criteria: transplant recipient, receipt of dialysis, substance abuse. Risk categories were stratified by flagging of high risk disease states such as congenital heart disease, malignant neoplasms etc. N=1,219,847 children

		occurring during stimulant use versus non, Hazard ratios were also applied.	
	Variables, Measurements	Findings	Future Implications
	Independent variables Age, stimulant use, presence of another high risk health condition, sex, race, state of residence, reason for eligibility for Medicaid **Dependent variables** Primary endpoints; cardiovascular risk as defined by sudden cardiac death, acute myocardial infarction, and stroke. Secondary endpoint; hospital admission for ventricular arrhythmia was added to capture negative chronotropic effects. Logistic regression was used to calculate propensity scores to estimate the likelihood of receiving stimulants. Separate regression models were used for each cohort group. Pearson's x2 was used to test proportion of covariates.	In the affected population, young children Caucasian males were overrepresented. This is consistent with other literature. Average duration of stimulant treatment was 1.2-0.6 months. There were 66 cases of sudden cardiac death, stroke, or acute MI. Event rate 2.8 per 100,000 patient years. Broken down by cohort group 3.5/100,000 for non-users 1.7/100,000 for current users 1.5/100,000 for former users 26 events occurred in high risk patients 63/100,000 patient years Stimulant use did not increase cardiovascular risk in this population Inclusion of the second endpoint; ventricular arrhythmia increased events to 95, but had similar offs ratios at the composite endpoint after censoring for	This was a large study representing more than a quarter of all US children. Similar to other smaller studies, despite a large sample size there were very few events. This study did not exclude high risk populations and accounted for them by stratifying the data points. None of the endpoints suggested any increased cardiovascular risk for patients taking stimulant medication for ADHD. Further research is needed to determine cardiovascular risk over time with long-term stimulant use.

		trauma and acute infection.	