

A SYSTEMATIC REVIEW OF THE LITERATURE ON THE ASSOCIATION  
BETWEEN EVIDENCE-BASED ADHD TREATMENT AND LATER  
ADOLESCENT/ADULT SUBSTANCE ABUSE

by

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## ABSTRACT

### A SYSTEMATIC REVIEW OF THE LITERATURE ON THE ASSOCIATION BETWEEN EVIDENCE-BASED ADHD TREATMENT AND LATER ADOLESCENT/ADULT SUBSTANCE ABUSE

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**Objective:** There has been much controversy over prescribing stimulant medication to treat the symptoms of childhood Attention Deficit Hyperactivity Disorder (ADHD). This study aims to explore the relationship between prescribing stimulant and non-stimulant medication for the treatment of childhood ADHD and future substance abuse in adolescents and young adulthood.

**Method:** A systematic review of all ten studies that met inclusion criteria was conducted testing whether stimulant treatment of ADHD reduces or increases the risk for future substance use, abuse and dependency. **Results:** Ten studies were critically appraised for high methodological quality. ADHD was found to be a high risk for subsequent substance use disorders. Stimulant treatment of ADHD in childhood was not found to increase the risk for substance use and, in fact, demonstrated a statistically significant protective effect against the development of future SUD in four out of the six studies. **Conclusion:** This study found that evidence-based treatment of ADHD in childhood does not increase the risk of substance abuse and does in fact protect

individuals from developing SUDs in adolescents and young adulthood. Furthermore this study has found a need for future research to be conducted in this area of study.

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CHAPTER 1  
INTRODUCTION

1.1 Background of the study

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurobehavioral disorder that is presented for treatment and is estimated to affect 4% to 9% of youths (Wilens, Faraone, Biederman & Gunawardene, 2003). ADHD is a debilitating disorder and contributes to multiple developmental problems for the child and can extend through childhood into adolescents and even adulthood. Thirty to fifty percent of ADHD symptoms persist into adulthood, with 11 to 31% of children with ADHD meeting criteria for Adult ADHD (Wilson, 2007). The DSM-IV-TR reports an extensive list of behavioral symptoms that are exhibited by children with the disorder. Children may demonstrate inattention difficulties through failing to give close attention to details or makes careless mistakes in schoolwork, have difficulties in sustaining attention in tasks or play activities or may appear not to be listening when spoken to directly. Hyperactivity may be manifested in fidgetiness, running or climbing in inappropriate situations, or talking excessively. Impulsivity is demonstrated by an individual who often blurts out answers before the question has been completed, has difficulties waiting turns or often interrupts or intrudes on others (American Psychiatric Association, 2000).

ADHD presents a very serious clinical and public health concern for our society because of the high risk for educational and occupational difficulties, family burden and stress and other behavioral problems which are often presented in children with ADHD. ADHD is a major risk factor in the development of Substance use Disorders. ADHD predicts an earlier age



of substance dependence onset, a more rapid transition from use to abuse and dependence and longer duration of substance abuse disorder (Wilson, 2007).

Evidence-Based treatment for ADHD is pharmacotherapy and, more specifically, stimulant medication. Stimulant medication is indicated in the treatment of ADHD, specifically for hyperactivity and impulsivity and inattentiveness as well as for the treatment of Narcolepsy. According to the practice parameters for the use of stimulant medications in the treatment of children, adolescents and adults (American Academy of Child and Adolescent Psychiatry, 2001), stimulants are among the most effective psychotropic medications in clinical use today. Wilens et. al (2003) stated that there has been more than 200 randomized trials consistently documenting the effectiveness of stimulant medication. Stimulant therapy has been found effective in the treatment of disruptive behavior since 1937 and has improved the affected child's compliance, academic tasks, and excessive motor activity in hyperkinetic children (AACAP, 2001). The most widely used stimulants used include Dextroamphetamine, Amphetamine-Dextroamphetamine, Methylphenidate, Vyvanse and Concerta. Vyvanse is the first pro-drug stimulant which is new on the market. It contains amphetamines however it is long acting and the body only uses what it needs curbing the potential for abuse. A pro-drug is a compound that does not exert its therapeutic effect until after the body has metabolized it (Manos, 2008). Other pharmacological therapies for the treatment of ADHD are: Strattera, which is a non-stimulant medication; Wellbutrin, an anti-depressant; and some anti-anxiety medications that have found to be effective when the first line medication has not worked.

### 1.1.1 Statement of the problem

With ADHD carrying an elevated risk for the development of alcohol and/or substance abuse disorders in adolescents and adults, smoking in adolescence, and antisocial behaviors throughout childhood, controversy surrounds the use of stimulant medication for the treatment of ADHD in childhood (Manos, 2008).

There has been a marked increase in stimulant use in the past two decades and this class of medication has become the most widely prescribed psychotropic medication for children with disruptive behaviors (Katusic, Barbaresi, Colligan, Weaver, Leibson & Jacobson, 2005). Concerns have been raised in the potential association of the treatment of ADHD with stimulant medications and the development of Substance abuse and the detrimental impacts that will be felt on the client, family, clinician and society (Wilson, 2007).

Stimulant therapy is the first line of treatment for ADHD. There are other treatment modalities available such as Strattera, a non-stimulant medication and psychosocial interventions, but there has been very little research done on how effective they are in treating ADHD. ADHD that is left untreated all together can have lifelong consequences on the child and family.

#### 1.1.2 Purpose of the study

The purpose of the study was to systematically assess the relevant research findings on the association of stimulant therapy in the treatment of ADHD in children and future substance abuse in adolescents and adults.

The following research questions will be answered through a systematic review of the literature:

- A) Does stimulant therapy treatment in children with ADHD increase the risk for substance abuse in adolescence and adulthood?
- B) Does non-stimulant medication for the treatment of ADHD in children reduce the risk for substance abuse in adolescents or adults?
- C) Does untreated ADHD lead to substance abuse in the future?

The hypotheses for this study are:

- A) Stimulant medication for the treatment of ADHD in children does not increase the risk of substance abuse in adolescents and adults.
- B) Stimulant medication for the treatment of ADHD in children will serve as a protective

factor for future substance abuse.

C) Non-stimulant medication in the treatment of ADHD in children will increase the risk of substance abuse in adolescents and adults.

D) Undiagnosed ADHD in children will significantly increase the risk for future substance abuse.

The future implications for the social work profession are discussed and the results from this research study will serve as a tool in the education of parents, clinicians, social workers and clients in effective and safe treatment of ADHD. Consultation with Dr. Alexa Osborne-Smith and with Dr. Bannister, the director of Mental Health with UTA University Health Services was made upon any pharmaceutical issues.

## CHAPTER 2

### LITERATURE REVIEW

A systematic literature review is the method of this thesis and will be included in the methodology section. A systematic literature review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review (Higgins & Green, 2009). A Systematic literature review is appropriate for this type of research because of the ability of this tool to summarize, appraise and effectively communicate the results and implications of large quantities of research. It is also valuable to use a systematic literature review because it can synthesize smaller studies which will vastly improve the quality of the research.

## CHAPTER 3

### METHODOLOGY

This chapter presents the research design, subjects, data collection procedures and analysis of data.

#### 3.1 Research Design

The study was carried out by a systematic review of studies that are relevant to the thesis topic. The systematic review was aimed to be comprehensive in its coverage of bibliographic sources that help to answer the research question.

##### 3.1.1 Search Strategy

In locating relevant articles, keywords and search strategies, a reference library professional was utilized as well as a comprehensive search of the following databases; MEDLINE, PsycINFO, PsychARTICLES, Academic Search Complete, Pub med, The Cochrane Library, Campbell Collaboration, Behavioral Science, The Cochrane Library of Systematic Reviews and Social Work Abstracts. Relevant pharmaceutical and substance abuse websites that were searched included; Shire biopharmaceuticals, Ortho-McNeil Pharmaceuticals, Atomoxetine hydrochloride website, Substance Abuse and Mental Health Service Administration website, RePORT(<http://projectreporter.nih.gov/reporter.cfm>) and National Institute on Drug Abuse website. The Belgium branch of the Cochran Collaboration, Belgium Centre of Evidence-Based Medicine, The Belgium Campbell Group, The South Asian Centre Cochran Database and other Non-US studies made available was searched for relevant articles

that were related to the thesis topic. A search of the grey literature, following references in identified articles and contacting experts in the field to identify additional studies including studies unpublished was also conducted. Key words that were considered include Attention Deficit Hyperactivity Disorder, Attention Deficit Disorder, children, adolescent, adults, stimulant medication, treatment, intervention, pharmacological, substance abuse, drug and alcohol use, substance abuse disorder, addiction, alcohol and drug abuse and chemical dependency.

### 3.1.2 Selection Criteria

In order to conduct a rigorous systematic review, exclusion and inclusion criteria were implemented to ensure the quality of the research appraised.

Exclusion criteria included studies done in languages other than English, narrative reviews, commentaries and other opinion based studies, weaker studies and multiple reports on the same set of data. Weaker studies include observational studies without control groups, uncontrolled experiment or those based on personal opinion. Studies that were more than 15 years old and articles that only provided an abstract only were excluded.

Inclusion criteria included all studies that utilize randomized controlled trials and meta-analysis. Other studies that were included were those conducted within the last 15 years, Cohort and Prospective studies, both published and unpublished articles and case-studies, and Clinical Trials. All full text articles and studies done in English and those translated from another language to English were also included.

### 3.2 Data Analysis

Critical appraisal of all studies include "PICO" to determine if the research question is focused and feasible to the study (Gambrill, 2006). Pico is a four part answerable question that describes the population of clients, the intervention of interest, what it may be compared to (including doing nothing), and hoped for outcomes (Gambrill, 2006). All studies collected will assess the methodology in terms of the strength of evidence. Randomized Controlled Trials are the strongest and most rigorous. All studies will be organized into a table or checklist with the

criteria for assessing the methodological rigor. Critical analysis of acceptable studies will include but not be limited to the following questions:

- A.) Did overview address a focused practice-related question?
- B.) Were search methods reported?
- C.) Was the search comprehensive?
- D.) Were the inclusion criteria reported?
- E.) Was validity criteria reported?
- F.) Was selection bias avoided?

Critical analysis of random controlled trials will include the following questions:

- A.) Was everyone in the study “blind” to treatment?
- B.) How was samples selected for trial?
- C.) Were subjects properly randomized into groups using concealed assignment?
- D.) Were the intervention and control groups similar at the start of the trial?

Blinding is a technique used in research to eliminate bias by hiding the intervention from the patient, clinician, and/or other researchers who are interpreting results ([www.cebm.net](http://www.cebm.net)).

Concealment is a process used to prevent foreknowledge of group assignment in a randomised controlled trial (Bandolier, 2007).

Critical Analysis of observational studies will include the following questions:

- A.) How were groups selected?
- B.) Is the intervention/treatment reliably ascertained?
- C.) Were groups comparable on all confounding factors?
- D.) Is their adequate adjustment for the effects of these confounding variables?
- E.) Were measures used valid?
- F.) Was outcome assessment blind to exposure status

According to Gambrill (2006), confounding variables are related to a casual factor of interest and some outcome(s) that are not represented equally in two different groups

## CHAPTER 4

### RESULTS

The purpose of the study was to systematically assess the relevant research findings on the association of stimulant therapy in the treatment of ADHD in children and future substance abuse in adolescents and adults.

#### 4.1 Research Questions

This study was guided by the following research questions:

- 1) Does stimulant therapy treatment in children with ADHD increase the risk for substance abuse in adolescence and adulthood?
- 2) Does non-stimulant medication for the treatment of ADHD in children reduce the risk for substance abuse in adolescents or adults?
- 3) Does untreated ADHD lead to substance abuse in the future?

#### 4.2 Research Hypotheses

The hypotheses for this study are:

- 1) Stimulant medication for the treatment of ADHD in children does not increase the risk of substance abuse in adolescents and adults.
- 2) Stimulant medication for the treatment of ADHD in children will serve as a protective factor for future substance abuse.
- 3) Non-stimulant medication in the treatment of ADHD in children will increase the risk of substance abuse in adolescents and adults.
- 4) Undiagnosed ADHD in children will significantly increase the risk for future substance abuse.



### 4.3 Analysis of Data

The results were analyzed by critically appraising all studies selected that fit the inclusion criteria. Critical analysis also appraised studies by proposing appropriate questions according to type of study.

### 4.4. Critical Appraisal

*Did the overview address a focused clinical question?*

Of the 27 studies collected, 13 sought to determine whether stimulant treatment for ADHD in children increases, decreases or does not affect the risk for subsequent substance abuse and substance use disorders. All studies included used the DSM definition of attention deficit hyperactivity disorder as a criterion for sample inclusion. While, Barkley et al. (2003), sought to determine the impact of stimulant treatment during childhood and high school on risk for substance use, dependency and abuse by young adulthood by examining the duration of stimulant treatment where else, Loney, Kramer & Salisbury (2002) examined whether ADHD children who were treated with stimulant medication become more involved with drugs then compared to ADHD children who are not treated with stimulant medication. Bukinstein (2008) examined the effects of stimulant medication treatment and the risk for future substance abuse as well as incorporating multimodal therapies.

*Were the Search methods reported and appropriate?*

In general, search methods were reported and were appropriate to the design used in each study. However, there were differences in inclusion due to the type of design. For example, Mannuzza, Klein, Truong, Moulton, Roizen, Howell & Castellanos (2008) used a prospective longitudinal study and were sufficient in their description of the groups and how they

were recruited. Wilens et al. (2003) inclusion criteria included prospective and retrospective studies, target population children, adolescents and adults with ADHD and had information on childhood exposure to stimulant pharmacotherapy, and used meta-analysis to evaluate the direction and strength of interventions. However, this study failed to locate or include studies in another language or translated to English.

*Was the search comprehensive?*

All studies analyzed were comprehensive in the trials depicted. References from studies were located and it is unlikely that any relevant trials were missed. Gibson, Bettinger, Patel & Crismon (2006) identified, reviewed and analyzed studies comparing Atomoxetine with Psychostimulant with the intent of determining the role of Atomoxetine in the pharmacologic management of attention deficit hyperactivity disorder and long term risk factors. MEDLINE was searched without language restrictions and used keywords including Attention Deficit Hyperactivity Disorder, ADHD, Atomoxetine, stimulants, Psychostimulant, methylphenidate and amphetamine salts. Gibson et al. (2006) also located relevant data presented at professional meetings that were attended and identified. Clinical studies comparing Atomoxetine and Psychostimulants, regardless of the study design, were evaluated and relevant efficacy and safety data from the studies were also included in the discussion.

Wilens et al. (2003) investigated all long-term studies in which pharmacologically treated and untreated youths with ADHD were examined for later SUD outcomes. Journal articles were searched through PubMed at the National Library of Medicine using ADHD, pharmacotherapy, stimulants and SUD as keywords. Wilens et al. (2003) also supplemented the search with additional data from scientific presentations at national and international scientific meetings.

Lambert (2005) analyzed the contribution of childhood ADHD, conduct problems, and stimulant treatment to adolescent and adult tobacco and psychoactive substance abuse.

Unfortunately, the study did not list the databases used to locate relevant studies which could be construed as not comprehensive but did identify methodological problems that could lead to possible differences in ADHD reported outcomes of ADHD samples. Key words used were ADHD, stimulant treatment, tobacco and substance use.

*For observational studies, was the procedure for sample selection reported?*

Overall, studies analyzed reported criteria that had to be met to be eligible in the study. For observational studies, identifying how participants were selected aim of the study conducted by Katusic, Bararesi, Colligan, Weaver, Leibson & Jacobsen (2005), was to evaluate the association between stimulant treatment and the risk for substance abuse among young adults with childhood diagnosis of attention-deficit/hyperactivity disorder (ADHD). This study was a population-based, birth cohort study that included all children born between January 1, 1976 and December 31, 1982 to mothers who, at the time of delivery, were residents of five townships with Olmsted County in Minnesota that constituted Independent School District (ISD) #535. Inclusion criteria that were identified included a series of five steps, with the first four screening for cases of ADHD and the fifth research diagnostic criteria were applied to all potential ADHD cases. Subjects had to meet DSM-IV criteria for ADHD, subjects had to have a positive ADHD questionnaire results and clinical ADHD diagnosis documented. Symptoms had to be noted by two or more different observers and last at least 6 months. Subjects in this study could not be considered an ADHD case if they had a diagnosis of a pervasive developmental disorder, severe mental retardation, schizophrenia or any psychotic disorder.

Barkley et al. (2003) study design was a 13-year prospective study. Inclusion criteria reported included a group rigorously diagnosed as hyperactive in childhood and a matched community control group. A childhood entry into the study required all studies to have an IQ >80, be free of gross sensory or motor abnormalities and be the biological offspring of their current mothers or have been adopted by them shortly after birth. The hyperactive group was

originally recruited from consecutive referrals to a child psychologist at Milwaukee Children's Hospital. To be considered hyperactive and eligible for the study, the inclusion criteria included that children have scores on both the hyperactivity Index of Revised Connors Parent Rating Scale and the Werry-Weiss-Peters Activity Rating Scale that met or exceeded to standard deviations above the mean of severity for same age-gender normal children, have scores on the Home Situations Questionnaire that indicates severe behavioral problems in at least 6 of the 14 situations on the scale of poor sustained attention, poor impulse control and excessive activity level, had developed their behavioral problems before age of 6, have had their behavioral problems for at least 12 months and have no indication of autism, gross brain damage, psychosis, thought disorder, epilepsy or mental retardation. Also, inclusion criteria included the clinical diagnosis based on the DSM-IV-TR.

*Was selection Bias avoided?*

One way that studies can reduce selection bias is by setting up specific selection criteria at the beginning thus reducing the risk of inclusion decisions being based on ideological views, personal preferences, convenience or other factors (Littell, Corcoran & Pillai, 2008). In general non-randomized studies are more prone to selection bias. Random controlled trials are the strongest research design that hold the least risk for selection bias but unfortunately, very few RCT's were located in the systematic review.

Allocation concealment refers to methods used to prevent the prediction of alternation of allocation sequences (Littell, Corcoran & Pillai, 2008). Biederman, Wilens, Mick, Spencer & Faraone (1999) incorporated blinding to the assessment personnel to both the control group and the psychiatric or pediatric ascertainment site. Also, all follow-up assessments were made blind to previous assessments of the same subjects and their family members to help reduce selection bias.

Random assignment is another method used to eliminate selection bias. According to Guyatt, Rennie, Meade & Cook (2008), random assignment is the allocation of individuals to groups by chance. The purpose is to eliminate selection bias and most threats of internal validity, so that between-group differences on outcomes are likely due to treatment conditions and not other factors. Mannuzza, Klein & Moulton (2003) used randomly assigned probands to methylphenidate treatment or matching placebo and comparisons. This study failed to describe the process they used to randomly assign the probands in the treatment or matching placebo group but did report that random assignment in the comparison group was done by random phone dialing as a way to identify the 34 Caucasian females with no behavior problems in elementary school.

*Was everyone blind to treatment in random controlled trials?*

In Mannuzza et al. (2003) study of whether stimulant treatment in childhood confers increased risk of substance use and abuse in later life, participants were blind to treatment. The results of this random controlled trial contradict the notion that stimulant treatment in childhood leads to substance abuse or use in later life which does not support the sensitization hypothesis that was tested in this study.

*Were the primary studies of high methodological quality?*

One limitation in this area was the lack of random controlled trials published. All studies included had used a control group and randomization which increased the strength of the study. Of importance was ensuring that studies used at least two independent evaluators and the interrater agreement assessed was adequate. Biederman et al. (1999) to increase the quality of their study used independent interviewers that help undergraduate degrees in psychology and were trained to high levels of interrater reliability. Interviewers were blind to family status, ascertainment site and were blind to previous assessments of the same subjects and their family members. Loney et al (2002) analyzed findings from earlier studies including the New Iowa Study. They studied 295 ADHD boys between 1954 and 1968, referred between ages 4

and12 to the University of Iowa child psychiatric clinic for outpatient evaluation and treatment, and followed up as young adults between ages 21 and 23. Patients were randomly assigned to one of the three supervising child psychiatrist all with different treatment preferences. Senior members of the research team were utilized to review all cases and all reviewers were blind to adult outcomes. Additionally, trained judges were also included to examine the psychiatric charts of all subjects rated and found that groups did not differ in their childhood behavioral symptoms but that the supervising psychiatrist described the boys differently because of differences in their psychiatric training, diagnostic beliefs and treatment philosophies. This difference between American and British experts in their diagnosis was well documented.

Publication bias occurs when the results of published studies are not representative of results of all completed studies (Littell, Corcoran & Pillai, 2008). Therefore inclusion of only published studies in a systematic review increases the risk of overestimating the outcome of the intervention. Publication bias was assessed in multiple articles and reported absent. Faraone & Wilens (2004) used the method of Egger to assess for publication bias. According to Faraone & Wilens (2004), this method regresses the standard normal deviate of the odds ratio (odds ratio divided by its standard error) against the precision of the odds ratio (inverse of its standard error). The findings were that the publication bias was not significant which indicated that the group of studies that controlled for baseline severity in this study had not overestimated the protective effect. Wilens et. al. (2003) reported publication bias to be absent in their study as well by using the method of Egger.

*Were the results from the studies combined appropriately?*

To ensure that studies were combined appropriately, studies were assessed to see if tests of heterogeneity were implemented. Wilens et. al. (2003) included 4 studies that they listed in tabular form and employed formal tests of heterogeneity. The trials in this study were statistically homogeneous, meaning that trials were sufficiently similar to be combined.

Barkley et. al. (2003) assessed for heterogeneity of the hyperactive group that was subdivided into those who had (N=98) and had not (N=21) been treated with stimulants in childhood. These two groups were compared using the  $X^2$  analyses on the proportion who self-reported whether they had ever used any of the 10 illegal or illicit drugs. All  $X^2$  tests were found nonsignificant.

Mannuzza et. al. (2003) looked at two treatment studies of Methylphenidate. In both studies, probands were randomly assigned to Methylphenidate or matching placebo. The 39 children from study 1 and 70 children from study 2 were highly comparable. There were no significant differences in the variable selected for inclusion thus these two studies were combined in the analysis.

*Do the conclusions match the data reported?*

Biederman et. al. (2008) examined the association between stimulant treatment in childhood and adolescence and subsequent substance use disorders into young adult years. The results of this study that assesses a longitudinal sample of male subjects diagnosed with ADHD in childhood and followed up for 10 years into their adulthood found that no prior treatment with stimulants was associated with subsequent increased or decreased risk for alcohol, drug or nicotine use disorders. Their findings support their research hypothesis and also represent the most methodologically rigorous assessment concerning the question of whether stimulant treatment increases the risks for future substance use disorders, with follow up into adult years and use of the proportional hazards survival models.

However, the present results of this study failed to replicate the previous 4 year follow-up study published on the same sample, which detected a protective factor of stimulant treatment. The study further hypothesizes that these discrepancies were the result of more

information gained through continued follow-up. A meta-analysis conducted by Wilens et. al. (2003) supported this hypothesis with results showing that stimulant-treated subjects were 5.8 times less likely to develop substance use disorders relative to untreated subjects in studies that extended their follow-up only into adolescence. Biederman et. al. (2008) also found this lack of protective effect of stimulants into adulthood was also seen in a study published by Faraone, Biederman, Wilens & Adamson, 2007. Biederman et. al. (2008) results were consistent with several other studies that failed to detect meaningful associations between stimulant treatment and subsequent substance use disorders.

Barkley et. al. (2003) examined the impact of stimulant treatment during childhood and high school on substance use, dependence and abuse by young adulthood. The results of this 13 year longitudinal study of hyperactive children followed into young adulthood (age 20-21 years) found very little support for the sensitization hypothesis or that the treatment with stimulant medication, either in childhood or in adolescence, contributed to a significant risk for lifetime substance use, dependency or abuse. These findings were consistent with 11 previous studies that also found no association of stimulant treatment to an increased risk of later drug use among children with ADHD but particularly for stimulants or cocaine.

Barkley et. al. (2003) analyzed three separate relationships, the first being the relationship of childhood stimulant use to adolescent self-reported drug use. The hyperactive group was divided into two subgroups and was compared using the  $X^2$  analyses. All  $X^2$  tests were nonsignificant. The second relationship analyzed was the contribution of childhood stimulant treatment to adult self-reported substance abuse. They computed the Pearson correlation coefficients of the hyperactivity group sample (N=119). And found that none of the correlation coefficients reached or even approached the traditional level of significance ( $P < .05$ ). The correlation coefficients ranged from -0.011 to 0.015. The final relationship analyzed was the contribution of stimulant treatment in high school to young adult drug use. Once again, they computed the Pearson correlation coefficients for the hyperactive probands who had (N=32) or



had not (N=115) been treated with stimulants in high school. None of the 10 correlations were significant (range= -.019 to .094).

Wilens et. al. (2003) investigated all long term studies in which pharmacologically treated and untreated youths with ADHD were examined for later SUD outcomes. Their conclusion supported their results that stimulant therapy in childhood is associated with a reduction in the risk for subsequent drug and alcohol use disorders. Wilens et. al. (2003) conducted a search of a total of 6 studies from the United States and Germany. The study provided odd ratios (ORs) that index the protective effect of pharmacotherapy on drug abuse or dependence and their 95% confidence intervals. In all 6 studies, the ORs indicated that there was an increased odds of not having an SUD for those subjects who were treated previously with medication.

Wilson & Levin (2005) reviewed the relationship between ADHD and early-onset SUD, recent clinical research developments related to the treatment of early-onset SUD, and risks and benefits of the treatment of adolescents with co morbid ADHD and SUD. Their review of the research found that ADHD, particularly with Conduct disorder, is a risk factor for SUD. Early identification and treatment of ADHD may reduce the risk of SUD, but more research is needed to verify this finding. Wilson & Levin (2005) reported results from a meta-analysis of seven prospective studies that found children with ADHD who were treated with stimulant medication were found to be 1.9 times less likely to develop SUD than those who are not treated. Because this was the only relevant study included in their research, the conclusion of this study supports the results reported.

Wilson (2007) examined ADHD and SUD and the impact of stimulant treatment. Wilson (2007) found several studies that supported the role of ADHD as a risk factor for the development of SUD. In relation to stimulant treatment and SUD risk in children with ADHD, one of the first studies to address this question was conducted in 1978 by Blouin, Bornatein and Trites, who found that medicated children later used more beer and wine than non-medicated

children. They also found that “good responders” to medication tended to consume less alcohol than “poor responders”. Another study reported by Wilson (2007) is one of the most cited recent studies that support the relationship among stimulant treatment and substance abuse was the “California community study” which followed 282 ADHD boys and girls into adulthood. This study indicated some increased risk of substance abuse in the stimulant-treated group however no statistically significant increase in risk was observed in this study.

Wilson (2007) also examined whether stimulant treatment reduces the risk for substance abuse. Wilson reported that animal studies showed some evidence of a sensitivity period 20-35 days after birth (roughly equivalent to rat adolescence) that suggests amphetamine exposure at 60 days of age may reduce the risk of later substance dependency. Wilson reported a prospective study of 219 boys who were treated with Methylphenidate as children. It was found that higher doses of Methylphenidate were associated with fewer diagnosis of alcoholism. Wilson included in his findings “The Iowa Study” which was a comprehensive longitudinal study of medicated vs. non-medicated youth that included a sample of 295 boys between the ages of 4 and 12. Participants were randomly assigned to psychiatrist who tended to prescribe either stimulant treatment or prefer non-stimulant treatment. This study found medicated subjects were significantly less likely to use non-medical stimulants, glue, LSD or opiates at the follow-up ages of 21-23. The study however was not a true randomization, and non-random factors could have influenced stimulant treatment in this study. Finally Wilson examined a meta-analysis conducted by Faraone and Wilens of 6 prospective and retrospective studies that represented all long term studies in which pharmacologically treated and untreated youths with ADHD were examined for later SUD outcomes. The meta-analysis included 674 medicated subjects and 360 un-medicated subjects. The results of the meta-analysis found a twofold reduction in risk for SUD in children treated with stimulants compared to untreated children. The follow-up study conducted in adolescence found a more robust protective effect than those conducted in early adulthood. The results of these studies that were included in

Wilson's research is consistent with his conclusion that all of the available studies, both pro and con, are limited by multiple factors, including a lack of randomization, lack of placebo control, failure to control for severity of ADHD and the possible presence of multiple confounding factors.

*Can the results be applied to my clients?*

The results of these studies cannot be applied directly to children, adolescents and young adults with ADHD, due to the limited number of random controlled trial located for review Mannuzza et. al. (2003), the only random controlled trial included reported data that contradicted the notion that stimulant treatment in childhood leads to substance abuse or use in later life which does not support the sensitization hypothesis. Most of the studies included consisted of prospective and naturalistic studies and some were able to use control groups but many lacked true randomization.

Data that were located give us promise that stimulant treatment for ADHD may serve as a protective factor for subsequent substance abuse. Furthermore, studies have concluded that stimulant treatment does not increase the risk for subsequent substance use disorder. A longitudinal case controlled study demonstrated that the findings revealed no evidence that stimulant treatment increases or decreases the risk for subsequent substance use disorders in children and adolescents with ADHD when they reach young adulthood (Biederman et. al., 2008)

## CHAPTER 5

### DISCUSSION

Stimulant treatment is the first line of treatment for children diagnosed with ADHD. Controversy has arisen over prescribing children a drug of abuse for fear of future development of substance use and/or abuse and dependency. While this research has looked specifically at a population of school age children through adolescents as well as young adulthood (up to age 25), many confounding variables may have impacted the results leading to an individual developing substance use disorders such as socioeconomic factors, genetics, and a diagnosis of ADHD itself.

The results of the studies evaluated suggest that stimulant treatment of childhood ADHD does not increase the risk for substance abuse in adolescents or in adulthood which supports this studies hypothesis. This is compelling research that contests the notion that stimulant treatment may indeed increase the risk for future substance abuse.

In addition to the findings supporting the first research hypothesis, research has also concluded that there is a protective factor in prescribing stimulant medication to children diagnosed with ADHD in developing future substance abuse in adolescence and early adulthood thus supporting the second hypothesis of this study. Wilens et. al. (2003) found 6 studies that reported compelling evidence that stimulant treatment seems to have a protective effect for adverse SUD outcomes in youths with ADHD.

Mannuzza et. al. (2008) found more than one dozen studies that have examined the association between stimulant treatment of ADHD and substance use disorder and with one exception, have not found a significant positive relationship. Mannuzza et. al. (2008) also did

not find a relationship between exposures to Methylphenidate and substance use disorders in children without ADHD treated with Methylphenidate or placebo.

No studies were located to determine whether non-stimulant medication for the treatment of ADHD reduces or increases the risk for substance use disorders. All studies located examined the efficacy of non-stimulant treatment on the core symptoms of ADHD but did not assess the relationship for future substance abuse.

#### 5.1 Implications for Future Research and Social Work Practice

Implications for future social work include more research with RCT. Since RCT's are the strongest form of evidence they will give an outcome of high validity. However it is important to look at the risk to the population being studied and it is important to not do any harm to the participants involved.

Further research will need to be conducted on adolescents and young adults with current substance use disorders who were left either untreated for their ADHD in childhood or treated by a non-stimulant medication (Atomoxetine). More research needs to be conducted on female subjects.

For social workers in clinic and school settings, children with ADHD are a substantial proportion of their caseloads: as much as 30 or 40% of clinic referrals (Corcoran & Walsh, 2006). This number is astonishing making it even more important that social workers are educated in the best treatment approaches for the treatment of ADHD.

Substance use and abuse disorders are highly prevalent in American society with an estimated 22 million Americans (9.4% of the total population age 12 and older) being reported in 2002 (Corcoran & Walsh, 2006). Adolescents have a 60% likelihood of being diagnosed with a psychiatric disorder along with a substance use disorder with ADHD being the most common (Corcoran & Walsh, 2006). Social workers are confronted with these clients in all types of

settings including schools, private practice and clinics and mental hospitals. Social workers will need to be trained in evidence-based treatments such as stimulant medication for the treatment of ADHD to effectively reduce the rates of future substance abuse.

Social workers will need to advocate for their clients whom have a diagnosis of ADHD to be provided effective and evidence-based treatment such as stimulant medication. Social workers should educate the clients on both the risk and benefits of stimulant medication and referring out to professionals when out of their field of knowledge. Clients should be made aware of all available research done on the effectiveness of stimulant treatment and this can be done by giving the client articles of studies as well websites that can be readily assessed by patients on pertinent information regarding the treatment in question.

## CHAPTER 6

### CONCLUSION

Attention Deficit Hyperactivity Disorder is the most common behavioral disorder of childhood (Sullivan & Rudnik-Levin, n.d.). Stimulant medication such as Methylphenidate is the first line of defense in treating the core symptoms of ADHD. Stimulant medication has been found to be the most effective way to treat the core symptoms of ADHD. The results of this systematic review suggest that stimulant treatment for children does not increase the risk for subsequent substance abuse in adolescents and young adulthood and furthermore evidence shows that stimulant treatment serves as a protective factor for individuals with the diagnosis of ADHD in developing substance use disorders, substance abuse and/or dependency.

APPENDIX A

STUDIES INCLUDED IN ANALYSIS



Author(s)/ year	Type of Study & Location	Purpose of study, technique & assessment tools	Population of study	Intervention & Comparators	Outcome	Conclusion & Limitations
Barkley, R.A., Fisher, M., Smallish, L., & Fletcher, K. (2003)	13 year prospective study Milwaukee Children's Hospital	To examine the impact of stimulant treatment during childhood and high school on risk for substance use, dependency, and abuse by young adulthood.  Evaluated participants at different time intervals and different ages (1979 to 1980 assessed at ages 4-12, then evaluated again between the years of 1987 to 1988 when part. Were 12 to 20 years and then in 1992 to 1996 when all were between 19 and 25)	Hyperactive children, adolescents and young adults (N=147)  Children ages 4-12 Adolescents 12-20 Adults 19-25  Controlled group (N=81)	Participants were rigorously diagnosed as hyperactive in childhood for inclusion.  Study followed groups for 13 years.  Participants were interviewed at different ages as well as parents.  Parent ratings were collected and structured interviews were conducted  Compared to a community controlled group (N=81)	All X <sup>2</sup> tests in the data for the relationship between childhood stimulant treatment and adolescent self-reported drug use were nonsignificant.  Pearson self-coefficients were computed between the parent-reported total duration stimulant treatment & frequency of self-reported drug use in young adulthood and none of the correlation coefficients reached or even approached traditional levels of significance (P<.05). Coefficients ranged from -0.11 to 0.15.	Concurs with 11 previous studies in findings that stimulant treatment of children with ADHD leads to an increased risk for substance experimentation, dependency, use or abuse by adulthood.  Very little support for the sensitization hypothesis.  Possible protective effect.  Did not attempt to verify the reports of parents or participants through med. Records. Results based solely on the subjective reports of these individuals.  Relatively small sample size of hyperactive children who had not been treated with stimulants in childhood (N=21) & small sample of same group that received stimulant treatment in high school (N=32).

Barkley, R.A., Fisher, M., Smallish, L., & Fletcher, K. (2003). Does the treatment of attention deficit/hyperactivity with stimulants contribute to drug use/abuse? A 13-year prospective study. *Pediatrics*, 111(1), 97-109.

Author(s)/ Year	Type of Study & Location	Purpose of study, technique & assessment tools	Population of study	Intervention & Comparators	Outcome	Conclusion & Limitations
Biederman, Wilens, Mick, Spencer, & Faraone (1999).	Longitudinal Massachusetts	Assess the risk on risk for SUD associated with previous exposure to psychotropic medication in boys with ADHD. Analyzed data from a longitudinal family genetic study of ADHD.  Various settings  Structured interviews  Interrater reliability  Assessment personnel were blind to family status and ascertainment site and all f/u assessments were made blind	Original sample included 260 families from psychiatric & non-psychiatric settings based on the ADHD status of an index child (140 subjects with ADHD and 120 normal control subjects).  All index children, white, non-Hispanic males 6 and 17 years of age at first assessment however the study restricted their analysis to male subjects $\geq 15$ years.	The cumulative incidence of SUD throughout adolescence was compared with Medicated subjects with ADHD (n=56), to non-medicated subjects with ADHD (n=19) and non-ADHD control subjects (n=137).	Un-medicated subjects with ADHD had significant increased risk for any SUD at follow-up compared with non-ADHD control subjects (adjusted OR: 6.3 [1.8-21.6]).  Subjects with ADHD medicated at baseline were at significantly reduced risk for a SUD at follow-up relative to untreated subjects with ADHD (Adjusted OR: 0.15[0.04-0.6]).	Consistent with findings in untreated ADHD in adults, untreated ADHD was a significant risk factor for SUD in adolescence and pharmacotherapy was associated with an 85% reduction in risk for SUD in ADHD youth.  Methodologic limitations including: Lack of ideal control group for assessing the independent effect of pharmacotherapy on SUD onset. Significant differences among medicated ADHD, un-medicated ADHD and non-ADHD control groups in age, SES, risk of conduct disorder and gender.  Lacked adequate statistical power to evaluate fully the effect on different subtypes.  Study can't make conclusions regarding the risk associated with stimulant treatment beyond the age of current sample, in females or in nonwhite subjects

Biederman, J., Wilens, T., Mick, E., Spencer, T., & Faraone, S.V. (1999). Pharmacotherapy of Attention-deficit/hyperactivity disorder reduces risk for substance use disorder. *Pediatrics*, 104(2), 3-5.

Author(s)/ Year	Type of Study & Location	Purpose of study, technique & assessment tools	Population of study	Intervention & Comparators	Outcome	Conclusion & Limitations
Biederman, Montuteaux, Spencer, Wilens, Macpherson. & Faraone (2008)	Naturalistic controlled 10-follow-up study. Massachusetts	Examine the association between stimulant treatment in childhood & adolescence & subsequent SUD (alcohol, drug and nicotine) into the young adult years.  Assessments made using COX proportional hazards survival models.  K-SADS-E for subjects < 18  Interviewers blind to subject's baseline ascertainment group, site & prior assignments.  Approx. 500 assessments from interviews of child & adult  Three-stage ascertainment procedure to select subjects in order to decrease false positives.	Caucasian male children with ADHD ages 6 to 17 (n=140).  Subjects from pediatric and psychiatric clinics.  Excluded were those children who were adopted or nuclear family was not available for study.  Male Caucasian youths without DSM-III-R ADHD (N=120)	10 year follow-up study.  SES measured using the 5-point Hollingshead scale  Stratified the ADHD subjects to lifetime history of receiving stimulant therapy.  Compared ADHD subjects with & Without a lifetime history of stimulant medication on follow-up demographic factors using Pearson Chi square tests and T tests for binary dimensional variables.	Of the 140 ADHD subjects recruited at baseline, 112 (80%) were successfully reassessed at the 10-year follow-up.  Cox proportional hazards models showed no statistical evidence for either increased or decreased risk for SUD in subjects who received stimulant treatment  No significant association between the duration of stimulant treatment and the risk for SUD.	No evidence that stimulant treatment increases or decreases the risk for subsequent SUD in children and adolescence with ADHD when they reach young adulthood.  Support the hypothesis that stimulant treatment does not increase the risk for subsequent SUD.  Failed to replicate their previous 4-year adolescent follow-up of the same sample, which detected a positive effect of stimulant treatment.  Results are consistent with several other studies that failed to detect meaningful associations between stimulant treatment & subsequent SUD.  It is unknown if results can be generalized to ADHD children in general population, other racial or ethnic backgrounds or to females.  Results suffer from misclassification to the degree that these ages were incorrectly recalled.  Lacked informative information you would get from a RCT.

Biederman, J., Monuteaux, M.C., Spencer, T., Wilens, T. Macpherson, H.A., & Faraone, S.V. (2008). Stimulant therapy and risk for subsequent substance use disorders in male adults with ADHD: A naturalistic controlled 10-year follow-up study. *American Journal of Psychiatry*, 165, 597-603.

Author(s) Year	Type of Study & Location	Purpose of study, technique & assessment tools	Population of study	Intervention & Comparators	Outcome	Conclusion & Limitations
Faraone & Wilens (2003).	<p>Meta – Analysis</p> <p>Of 7 long-term studies (&gt;4 years)</p> <p>Between the years of 1999-2003</p> <p>Sensitivity analysis by re-computing meta-analysis after deleting one study at a time.</p> <p>Harvard Medical School Boston</p>	<p>To examine the relationship between the treatment of ADHD with stimulants &amp; SUD by reviewing their published meta-analysis of 6 studies &amp; adding preliminary data from a 7<sup>th</sup> study.</p> <p>Available studies that sought to measure the extent of exposure to which stimulant treatment in childhood is associated with SUD in adolescence and young adulthood.</p> <p>Studies reviewed all naturalistic</p>	<p>Medicated subjects (n=766)</p> <p>Untreated subjects (n=429)</p> <p>Number of total subjects (N=1195)</p> <p>Most male</p> <p>Adolescence</p> <p>Adults</p>	<p>Random effects meta-analysis</p> <p>2 X 2 table classifying subjects by treatment status-pharmacological or not- &amp; the subsequent development of SUD present or not from which to compute the odds ratio.</p> <p>Method of Carlin</p>	<p>Of the 766 medicated subjects in the 7 studies combined, 98% treated with stimulants.</p> <p>Did not report findings on overall substance abuse but only data on cocaine abuse</p> <p>A statistical significant pooled odds ratio of 2.0 (z=2.4, p=.02) indicating an overall protective factor of stimulant treatment on subsequent substance abuse</p> <p>P values &lt;.05</p> <p>No significant statistical differences between the odds ratios for drug and alcohol outcomes (2.4 vs. 4.0, z=1.1, p=.3)</p> <p>Studies that reported follow-up into adolescence showed a greater protective effect (OR=5.8) than those followed into adulthood (OR=1.7, z=4.4 p&lt;.0001)</p>	<p>Meta-analysis indicated that pharmacotherapy of ADHD does not increase the risk for subsequent SUD.</p> <p>Protective factor for subsequent SUD</p> <p>Stimulant therapy reduces the risk for SUD by half, reducing the risk for subsequent SUDs in ADHD youths to levels well within accepted population risks.</p> <p>The number of studies suitable for selection into the study was small (N=7) as was the number of subjects (N=1195).</p> <p>Most subjects were male</p> <p>No randomized studies</p> <p>Several confounds-severity of illness, co morbidity, family history of SUD may have independently effected outcomes.</p> <p>4% of treated sample were not treated with stimulants</p> <p>The duration of therapeutic regiment was not delineated.</p>

Faraone, S.V., & Wilens, T. (2004). Does stimulant treatment lead to substance use disorders? *Journal of Clinical Psychiatry*, 64(suppl. 11), 9-13.

Author(s) Year	Type of Study & Location	Purpose of study, technique & assessment tools	Population of study	Intervention & Comparators	Outcome	Conclusion & Limitations
Fisher, & Barkley (2003)  Supported by an unrestricted educational grant from McNeil Consumer & Specialty Pharmaceuticals	Controlled longitudinal Study  13 year  Milwaukee	Address relationship between stimulant treatment for ADHD and psychoactive SUD  A treated group & a community controlled group  Structured clinical interview for DSM-III-R, Non-patient edition.  Parent ratings, self-reports, Multiple rating scales & Indexes	Hyperactive children (N=158)  Matched Normal Community control group of children (N=81)  Male subjects 91% White subjects 94%  Adolescents @ follow-up (mean age 15 years) (N=123) & treated with stimulants at follow-up (N=98)  Young adult (Mean age 21 years) (N=147 & Young adults treated with stimulants (N=32)	Comparison of subjects treated and untreated with reference to their adolescent reports of ever have tried 10 illicit substances (cigarettes, alcohol, hashish, heroin, hallucinogens, non-prescribed stimulants, sedatives, tranquilizers)  Comparison of treated & untreated subjects. with respect to their young adult self-reports of drug use  The frequency of (SU) & categorical use of the 10 identified drugs was correlated with the duration of stimulant treatment for ADHD compared between subjects who had been treated with stimulants through the high school years & those who had not.	no significant results when treated and untreated subjects were compared on frequency measures of drug use (using log-transformed) & Cocaine use was marginal (P=.06), then reanalyze with potential mediators the results were nonsignificant (P=.16)  No significant correlation was found in duration of stimulant & 10 frequency measures of drug use or in self-report of adolescents trying drugs.  98 treated subjects were divided into those whose treatment had lasted 1 year or more (N=55) & those whose lasted less than 1 year (N=43). The results indicate there is no increased risk for (SU) by adolescents who were treated with stimulants for more than 1 year compared to those treated for less than 1 year.	Data show stimulant therapy for ADHD in childhood is not associated with an increased risk of adolescent experimentation with (SU), frequency of such use, or the risk of developing SUD by young adulthood.  The duration of stimulant therapy was not associated with a risk for any form of substance use in adolescents or adulthood  A protective effect of developing hallucinogen abuse only.

Fisher, M., & Barkley, R. A. (2003). Childhood stimulant treatment and risk for later substance abuse. *Journal of Clinical Psychiatry*, 64(suppl.11), 19-23.

Author(s) Year	Type of Study & Location	Purpose of study, technique & assessment tools	Population of study	Intervention & Comparators	Outcome	Conclusion & Limitations
Katusic, Barbaresi, Colligan, Weaver, Leibson & Jacobsen (2005)	Population-based cohort  Rochester, Minnesota	Evaluate the association between stimulant treatment & the risk for substance abuse among young adults with a childhood diagnosis of ADHD  School and Medical records, school assessment & reassessment information, education intervention plans & notes  Multistage stepwise approach  DSM-IV	Children born between January 1, 1976-December 31, 1982 to mothers who at the time of delivery were residents of 5 townships within Olmsted County that constitutes ISD # 535(N=8548)  Target population consisted of 5718 children(2956 boys & 2762 girls) @ or after 5 years of age live in Rochester  Median age at follow-up was 18.3 for both ADHD cases & controls	For each ADHD cases, 2 matched controls (n=758) were selected from the birth cohort (n=5718).  Association between ADHD case status & the risk of substance abuse was evaluated by logistic regression models, with & without adjusting for the matching factors(gender & year of birth) & duration of follow-up(birth until emigration, death, school graduation or drop-out)  Evaluation of treatment with stimulant medication & substance abuse evaluated with logistic regression models, by gender, with & without adjusting for year of birth & duration of follow-up.	ADHD cases were 6.2% more likely (95%CI=4.0-9.4; p<0.001) to have alcohol/drug abuse documented in their medical and/or school records than controls)  Among the 379 ADHD cases, 21.9% had documented substance abuse compared to 4.4% of the control subjects.  Boys ADHD cases were 6.3 times (95%CI=4.0-10.1; p<0.001) more likely than controls to have substance abuse documented in their records.  Girl subjects with ADHD were 5.9 times (95% CI=2.0-17.0; p<0.001) more likely than controls to have substance abuse documented in their records.  20.3% of the cases treated with stimulants had documented substance abuse compared to 27.4% of ADHD cases not treated (OR=0.7;95% CI=0.4-6.1;p=0.53)  Protective effect apparent among boys treated with stimulants (OR=0.5; 95% CI=0.3-0.9;p=0.027)	Subjects with ADD are 6.2 times more likely to have alcohol/drug abuse documented in their medical and/or school records than the matched controls.  Stimulant treatment does not increase the risk for alcohol/drug abuse for children with ADHD overall and for boys.  Considerable emigration (43%) of the original 1976-1982 birth cohort of 8546.  Potential bias's have been addressed.  Did not directly address the study subjects.  Confounding factors were not addressed.

Katusic, S.K., Barbaresi, W.J., Colligan, R.C., Weaver, A.L., Leibson, C.L., & Jacobsen, S.J. (2005). Psychostimulant treatment and risk for substance abuse among young adults with a history of ADHD: A population-based, birth cohort study. *Journal of Child and Adolescent Psychopharmacology*, 15(5), 764-776.

Author(s) Year	Type of Study & Location	Purpose of study, technique & assessment tools	Population of study	Intervention & Comparators	Outcome	Conclusion & Limitations
Lambert (2005)	28 year prospective longitudinal study  Randomly Sampled  Controlled for age and sex  Alameda & Contra Costa Counties in the East Bay Area of San Francisco	Examines the contribution of childhood ADHD, conduct problems and stimulant treatment to adolescent and adult tobacco and psychoactive substance abuse.  Children's Attention & Adjustment Scale (CAAS)  Teachers rating scales of cardinal symptoms of ADHD  Interviews with parents and participants  DSM-IV  Examined at different years	Children (N=492)  Children whom met hyperactive diagnosis but untreated controls (n=68)  Behavior control group (n=59)  Treated hyperactive & diagnosed children (n=214)  Age mate control subjects (n=159)  Females (n=108)  Ethnic minority groups (n=114)  Children from randomly assigned classrooms grade kindergarten through 5 <sup>th</sup> in private, public and paraxial schools  No clinic referred participants.	Followed-up at different years  28 year duration  Linear hierarchical regression analysis  Analysis of variance for stimulant treatment vs. no treatment.  Chi Square analysis  Compared treated vs. untreated and a control group	Chi square analysis was significant for the association between ADHD and tobacco dependency (p≤.001) and Cocaine dependency (p≤.01) and amphetamine dependency (p≤.10) and approach significance for alcohol dependency (p≤.10) but not marijuana dependence.  Chi square analysis supporting an association of stimulant treatment and substance dependency were significant for tobacco dependency (p≤ .001) and cocaine dependency (p≤.01)  Stimulant treatment 1 year or more (Tobacco OD=1.0, Cocaine OD=2.3 & Cocaine/Amphetamine OD=1.9)	Stimulant treatment may be a sensitizing agent in adult dependence and heavy use of psychostimulants  Those with childhood ADHD may self-medicate in adulthood with psychostimulants and become dependent on them.  Lack RCT

Lambert, N. (2005). The contribution of Childhood ADHD. Conduct problems and stimulant treatment to adolescent and adult tobacco and psychoactive substance abuse. *Ethical Human psychology and Psychiatry*, 7(3), 201-221.

Author(s) Year	Type of Study & Location	Purpose of study, technique & assessment tools	Population of study	Intervention & Comparators	Outcome	Conclusion & Limitations
Loney, Kramer & Salisbury (2002)	Review of existing studies  Iowa  California  Canada	To determine whether ADHD children who are treated with stimulant medication become more involved with drugs than comparable ADHD children who are not treated with stimulant medication  Studies comparing ADHD treatment vs., non treatment of ADHD with stimulants.  Reviewed older studies and newer studies.  Medicated Attitude Interview  Medication Experience Questionnaire  Licit-Illicit Drug Scale (LIDS)  DSM-III	Different samples located  Iowa Study N=295 ADHD boys between the ages of 21 and 23  98% white  California Study N=282 boys and girls  Adolescents	Comparison of studies  Medicated children compared to un-medicated children and development of substance abuse  Comparison of subjects at different years of their lives.  Iowa study used random assignment to refer samples to three psychiatrists where two of the psychiatrist recommended stimulant medication for 63% of their young patients and the third only recommended stimulants to 3% of his.  Reviewers blind to adult outcomes in the Iowa study.  Logistic regression analyses	Failed to find increased drug involvement in medicated hyperactive individuals from Canada although both the Canadian and subsequent American studies found that fewer medicated ADHD children than normal ones later tried hallucinogens.  California study reported that adults who were medicated as children for ADHD were more likely to be dependent on tobacco and cocaine than were adults who were not medicated however these differences did not reach conventional levels of statistical significance (Tobacco p<.08; cocaine p<.13), and the difference between medicated and unmedicated individuals in adult dependence on stimulants was reported as not significant.  At ages 21 and 23, medicated ADHD boys in the Iowa Study were significantly less involved than unmedicated ones with tobacco, nonmedical stimulants, glue and opiates  38% of medicated subjects had tried nonmedical stimulants compared to 58% of unmedicated subjects (and 35% of normal classmates)  No significant differences between medicated and unmedicated ADHD in adult involvement with cocaine or in subsequent diagnoses or drug abuse disorder.  Findings indicate that the risk of adult drug involvement and related psychiatric disorders is greater for children who are not medicated than for children who are.	Untreated ADHD was a significant risk factor for SUD in later adolescence.  Pharmacotherapy treatment for ADHD was associated with an 85% reduction in overall likelihood of subsequent SUD.  Limitations: All male subjects  No RCT  Lack of appropriate Prospective studies of long-term effects of treatment.  Small sample sizes in studies reviewed.

Loney, J., Kramer, J.R., & Salisbury, H. (2002). Medicated Vs. unmedicated ADHD children-Adult involvement with legal and illegal drugs. In P.S. Jensen & J.R. Cooper (Eds.). *Attention deficit hyperactivity disorder: State of Science best Practices* (pp.17-1-17-16). Civic Research Institute, incorporated.



Author(s) Year	Type of Study & Location	Purpose of study, technique & assessment tools	Population of study	Intervention & Comparators	Outcome	Conclusion & Limitations
Mannuzza, Klein & Moulton (2003)  Supported in part by PHS grant MH-18579 by MIMH and by PHS grant DA13910 from NIDA	Controlled prospective follow-up  Randomized Trial	Examines whether stimulant treatment in childhood confers increased risk for Substance use and abuse in later life, as the sensitization hypothesis predicts.  Probands blind to group and treatment status  Performance Wechsler Intelligence scale for Children  Wechsler Intelligence Scale for Children-Revised  Conners Hyperactivity Factor  Schedule for the Assessment of Conduct, Hyperactivity, Anxiety, Mood and Psychoactive Substances  Interrater reliability kappa for SUD was 0.80  Coding characteristics of use and abuse	Probands:  Caucasian children between the ages of 7 and 13 (n=109)  Boys (n=79) & girls (n=30)  Children referred by teachers because of academic difficulties  Comparisons: Caucasian males with no behavior problems prior to age 13 (n=100) & Caucasian females in elementary school (n=34)  Adult follow-up: N=13  Methylphenidate group (n=6) & Placebo group (n=7)	16 years  Children ages 7-12, with developmental reading disorders but no psychiatric diagnoses were randomly assigned to methylphenidate treatment (n=43) or matching placebo (n=66) for 12-18 weeks.  At 16-year follow-up, 94% of probands and 129 normal comparisons were evaluated  Children did not receive medication beyond their study treatment.	16 year follow-up: No significant differences between groups on the prevalence of SUD(abuse or dependence) for any of the 7 drug categories studied  Methylphenidate-treated and placebo probands did not differ significantly on the use of any substance. Significantly more comparisons had used stimulants than either of the methylphenidate-treated or placebo proband groups (60% vs. 46% and 41% respectively).	Contradicts the notion that stimulant treatment in childhood leads to substance abuse or use in later life.  Sensitization hypothesis not supported.  Only study in which treatment with methylphenidate was randomized and provides convergent support that exposure to stimulants in childhood does not increase the risk for the later development of substance use or abuse.  Small samples size did not allow for examination of specific age effects needed to determine if stimulant treatment in childhood served as a protective factor against later SUD.  Duration of childhood treatment was brief and results may differ with longer treatment periods.  Sample size of treatment groups was small which reduced the power to detect significant differences.

Mannuzza, S., Klein, R. G., & Moulton, J.L. (2003). Does stimulant treatment place children at risk for adult substance abuse? A controlled prospective follow-up study. *Journal of Child and Adolescent Psychopharmacology*, 13(3), 273-282.

Author(s) Year	Type of Study & Location	Purpose of study, technique & assessment tools	Population of study	Intervention & Comparators	Outcome	Conclusion & Limitations
Wilson, Levin (2005)	Review Of retrospective, prospective & meta-analysis	Exploration of theoretical mechanisms that may explain the relationship between ADHD and SUD  Stimulant treatment risk or protective factor discussed	Different samples depending on the studied reviewed.  Children, adolescent and adults  Samples with ADHD and those with SUD	Samples treated with stimulant medication vs. untreated  Sample treated with non-stimulant medication  Treating active SUD and ADHD with stimulants vs. nonstimulants	A Meta-analysis reviewed of 7 prospective studies found that children with ADHD who were treated with stimulants were 1.9 times less likely to develop SUD than those who are not treated (Farone & Wilens, 2003).  Adults diagnosed with ADD in childhood –who had used stimulant medication in childhood—are more likely to be daily smokers and tobacco dependent than those who had not taken stimulants.  Both animal and human models suggest that early exposure to amphetamines may, in fact, reduce sensitivity to the development of amphetamine dependence.	Early identification and treatment of ADHD may reduce the risk of SUD but more research is needed to verify this study's findings.  Discussion of selection bias  Methodological limitations include randomization and control groups.

Wilson, J. J., & Levin, F. R. (2005). Attention Deficit/Hyperactivity Disorder and early onset substance use disorders. *Journal of Child and adolescent Psychopharmacology*, 15(5), 751-763.

Author(s) Year	Type of Study & Location	Purpose of study, technique & assessment tools	Population of study	Intervention & Comparators	Outcome	Conclusion & Limitations
Wilens, Faraone, Biederman, Gunawardene (2003)	Meta-analysis 6 studies Massachusetts PubMed.	Concerns that stimulant therapy of youths with ADHD may result in an increased risk for SUD  Systematic literature search of all available prospective and retrospective studies of children, adolescents and adults with ADHD  2X2 tables classification subjects by treatment status and the subsequent development of SUD using the Odds ratio  Random-effects meta-analysis to analyze the ORs using the method of Carlin  Method of Egger  Test for heterogeneity  Coding characteristics of use and abuse	Medicated subjects (n=674)  Unmedicated subjects (n=360)	Comparison between groups at baseline  Sensitivity analysis	ORs indicate the increased odds of not having an SUD for youths who were treated previously with medication.  7 of the ORs (from 4 studies) are >1.0 suggesting a protective effect of stimulants & Five of ORs are statistically significant.  Pooled estimate of the OR was 1.9 and was statistically significant (z=2.1; P=.037; 95% CI for OR: 1.1-3.6)  Greater protective effect (OR=5.8) in adolescent follow-up than in those studies followed into adulthood.	Treatment for ADHD significantly decreases the risk for subsequent SUD.  4 of the 6 studies identified striking protective effects of stimulant medications for ADHD on subsequent SUD.  2 of the studies showed significantly reduced SUD risk in adolescence.  Studies reviewed were naturalistic and not randomized at baseline to medication  Possible publication bias  Paucity of research data available for review (n=6 studies)  Naturalistic nature of studies may have created confounds that may independently affect outcome

Wilens, T. E., Faraone, S.V., Biederman, J., & Gunawardene, S. (2003). Does stimulant therapy of ADHD beget later substance abuse? A meta-analytic review of the literature. *Pediatrics*, 111(1), 179-185

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