

## REVIEW

# Age of amphetamine prescription and ADD/ADHD: Younger is Better

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Over the past few decades, the prescription of stimulants to treat disorders such as attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) has risen. The addictive nature of these stimulants, especially that of amphetamine and its derivatives, has raised concern in the scientific community over whether stimulants as a treatment are effective in improving the long-term quality of life in individuals diagnosed with attention deficit disorders or whether they potentially lead to abuse of other substances. Specific concern has been raised as to whether stimulants might specifically contribute to co-morbidity between ADD/ADHD and Substance Use Disorder (SUD). While separate groups have come to varying conclusions regarding the effectiveness of stimulant treatment for ADD and ADHD, many of the studies that conclude a beneficial effect possess a large degree of confounding factors and conflicts of interests. This review addresses the nature of stimulant prescription and the research surrounding it, and concludes that prescription of amphetamines for treatment of attention deficit disorders is effective if initiated at younger ages, but can possibly lead to abuse of nonprescription stimulants if initiated in the teen years.

## Introduction

Among school-aged children, ADHD is one of the most common psychiatric disorders. Estimates have placed the prevalence of ADHD as high as 3-7% of all children in the United States, with as many as 37-85% of these cases persisting into adulthood<sup>1</sup>. Pharmacotherapeutic treatment of ADHD typically begins when a patient is 9.8 to 10.6 years old, with a duration of 33.8 to 42 months<sup>2</sup>. Treatment is most commonly prescribed to individuals that are 10-14 years old and is usually made available to the individual or to the parents of the individual until graduation from high school or college<sup>2,3</sup>.

The most-prescribed stimulant for ADHD is methylphenidate (Ritalin); however, amphetamines (mostly dextroamphetamine) account for about one-third of all ADHD treatment prescriptions<sup>2</sup>. Biologically, methylphenidate interacts with the dopamine transporter to block dopamine reuptake, thus increasing dopamine in the synaptic cleft. Amphetamines also interact with the dopamine transporter but via an efflux mechanism, reversing the direction that the transporter conducts dopamine. Both methylphenidate and amphetamine increase the amount of dopamine in the synaptic cleft of the mesocorticolimbic system, resulting in an increased level of attentiveness that is beneficial to those with ADD or ADHD.

In terms of treatment of ADHD, stimulant treatment such as methylphenidate and methamphetamine is considered to be the first

line of defense in ADHD therapy. This type of treatment is frequently attempted before other methods of intervention, such as counseling or non-stimulant medication<sup>4,5</sup>, and in the short term, stimulant treatment of ADHD has proven effective, with 73% of cases reporting treatment to be “favorable and effective” and only 22% reporting minor side effects<sup>2</sup>. In combination, prescription of amphetamines has increased greatly during the past 20 years, especially among young children and those over 14.6. Prescription of amphetamines to two-to-four year olds increased 380% between 1990 and 1997, while prescription to those older than 14 increased 817%<sup>3</sup>.

Given the young age of treatment onset and the duration for which the drug is made available to ADHD patients, along with the prevalence of its clinical use, some critics have raised concern in scientific literature over excessive stimulant use and the long-term effects of stimulants on children<sup>2,7,8</sup>. Such concern is bolstered by the strong correlation between ADHD and Substance Use Disorder (SUD), the repeated abuse or dependence on a substance that alters the central nervous system for the purpose of obtaining its mind-altering effects or avoiding a withdrawal. For instance, adolescent tobacco use has been shown to be significantly higher amongst those with ADHD<sup>9</sup>. Alcohol abuse is associated with as many as 17% to 45% of ADHD adults, while drug abuse is seen in 9 to 30%, suggesting that ADHD patients are at

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a significantly higher risk than the general population<sup>9</sup>. Specifically, adolescents with ADHD have been calculated to be more than three times as likely to use marijuana when compared to the general population, and a striking 39.1% of ADHD patients older than 13 responded in a survey that they had abused nonprescription stimulants—mostly cocaine and methamphetamine<sup>9-11</sup>.

Moreover, amphetamines are reinforcing. Following use of an amphetamine, an individual will be more likely to use the drug again if given the opportunity. This property can lead to abuse and drug-seeking behavior<sup>13,14</sup>. It follows that amphetamine treatment may contribute to general drug-seeking behavior and substance abuse in ADHD individuals and may especially raise the risk of non-medical stimulant abuse. However, other studies have also implied that stimulant treatment, including treatment with amphetamines, may lower the likelihood of an individual with ADHD to “self-medicate,” thus lowering the potential for drug abuse in adolescence and adulthood<sup>16</sup>. Based on these few population-level studies and meta-analyses, a portion of the medical community has come to the conclusion that treatment of ADD or ADHD with amphetamine is beneficial for the majority of patients. However, these studies have a number of weaknesses that will be addressed in this review.

### Stimulant Treatment Increases Potential for Drug Abuse

Animal studies have shown that amphetamine treatment of ADHD may increase susceptibility to substance abuse, demonstrating the abuse potential that amphetamines pose. For instance, several animal studies have demonstrated that amphetamine exposure induces drug cravings in rats<sup>14,16</sup>. One such study illustrated that rats treated with amphetamine tended to have higher levels of self-administration of cocaine, suggesting that prescription of amphetamines may raise susceptibility to non-prescription stimulant drug abuse in human patients<sup>16</sup>. A similar study concluded that self-administration of amphetamine led to sensitization (an increased response to the same dose of the drug) of its rewarding effect, as well as to the rewarding effects of both cocaine and morphine<sup>14</sup>. Since sensitization of reward may play a major role in the development of drug-craving and dependence, amphetamines, therefore, seem likely to increase a patient's sensitization to his or her own prescription<sup>15</sup>. This may then lead patients to illicit nonprescription drugs to fill the void of reward that their treatment once occupied. Thus, a patient's prescription would increase the likelihood of abuse of both amphetamines and almost any other drug with reinforcing properties. In particular, drugs with similar stimulant properties that activate the mesocorticolimbic dopaminergic system, such as nicotine, cocaine, and methamphetamine, are strong candidates for abuse following amphetamine treatment.

Moreover, abuse of non-medical stimulants may stem directly from dependence on ADHD medication. Studies of ADHD patients found that 15%-25% reported having abused their medication recently, via crushing and snorting the pills or taking a higher-than-prescription dose for recreational purposes<sup>9,11,17,18</sup>. One group discovered that the most important factor in the development of abuse of prescription amphetamines was the abuse of other substances<sup>16</sup>, implying that substance abuse may lead to abuse of medication. However, the data in this study can be interpreted to imply reverse causation; given the sensitizing and reinforcing nature of amphetamines, patients may become dependent on their medication and turn to other substances after their medication no

longer gives them satisfaction.

Furthermore, the abuse of ADHD treatment seems to be much higher for amphetamines when compared to methylphenidate. Researchers have found that the most-abused medications used to treat ADHD were mixed amphetamine salts, constituting 40% of all abused ADHD medication, while long-acting amphetamines constituted an additional 12% of abused medication. Therefore, amphetamine abuse alone constituted 52% of prescription medication abuse<sup>11</sup>. Since only one-third of stimulant medication prescribed for ADHD treatment is amphetamine-based, it is apparent that amphetamines have a higher potential for abuse than other ADHD treatments. Thus, the animal and population studies detailed above both found an increase in stimulant abuse amongst ADHD patients treated with stimulants.

Lastly, population studies also found that increased drug abuse following amphetamine prescription was specific to stimulant abuse. In a study that followed 21 untreated and 98 treated ADHD patients into adulthood, a significant increase in cocaine use was found amongst those treated with stimulants<sup>19</sup>. Other studies found that both nicotine and cocaine use were increased amongst ADHD patients that were treated with stimulants<sup>20,21</sup>. However, it was also found that depressants such as marijuana and alcohol showed no increase in abuse potential, supporting the hypothesis that amphetamine and/or stimulant prescription specifically raises the risk of non-medical stimulant abuse via sensitization<sup>20,21</sup>.

### Age of Treatment Onset Affects Likelihood of Drug Dependence Development

It has been hypothesized that stimulant treatment is increasingly protective against drug abuse in adult life the earlier the medication is prescribed in childhood<sup>22</sup>. This hypothesis ties into a study that assessed “quality of life” based on measures of alcoholism, substance abuse, criminality and a questionnaire in adults with ADHD who had previously been treated with stimulants versus those that had not. This study found that ADHD patients treated as children had a higher quality of life than those treated in adolescence by the researcher's measured index<sup>23</sup>.

This hypothesis - that onset of treatment at a younger age correlates with effectiveness of treatment - may indicate a link between age of prescription and likeliness to experience SUD. A younger child is much less likely to have access to any form of street drug, especially stimulants such as cocaine or methamphetamine<sup>24</sup>. If prescribed at a younger age, amphetamine sensitization would occur during a time in the child's life in which they would have no outlet through which to act on drug cravings. Since the average duration of treatment lasts between 33.8 to 42 months, the medication would likely stop before the child reaches adolescence<sup>2</sup>. Withdrawal, a series of negative symptoms that occur in the absence of a drug after a prolonged period of abuse, would therefore occur when the individual would most likely have limited access to illegal stimulants. As a result, a young child treated with amphetamines would not necessarily have an increased risk for abuse of other stimulants by the time he or she reached adolescence - when illicit drugs are more readily found.

In contrast, if the onset of treatment were to start in the early teens (12-15 years old), drug-seeking behavior would peak just as illicit substances became more available. This hypothesis is supported by one study that found that ADHD individuals whose

treatment persisted into adolescence were more likely to become dependent on cigarettes than those whose treatment ended earlier<sup>25</sup>. The individuals whose treatment had stopped before adolescence went through the sensitization/withdrawal process before cigarettes became available to them, either through legal or illegal means.

The effect of amphetamine is also hypothesized to be greater under both temporal and environmental cues previously associated with administration<sup>26</sup>. It is likely that a child treated at a younger age would move out of an environment previously associated with amphetamine (such as moving from middle school to high school) and therefore have a decreased sensitivity to amphetamine at an older age compared to an individual who started treatment in adolescence. The child treated at a younger age would therefore be less likely to abuse their prescription and eventually other illicit drugs. Thus, ADHD treatment at a younger age seems to have little or no effect on drug abuse during adolescence and adulthood, while treatment that continues into adolescence may raise the risk of non-prescription stimulant abuse.

Lastly, adolescents typically experience much more stressful environments as more responsibility is given to them at both home and school. The stress of adolescence may synergize with the effects described above, and thus further increase the likelihood of stimulant abuse. On the other hand, if amphetamine prescription is initiated before adolescence, the individual will not have the same added level of stress, and thus will be less driven to abuse their medication or drugs with similar effects.

### **Evidence that Amphetamine Prescription Reduces Drug Abuse Potential**

Although much evidence points to an increased risk of substance abuse with amphetamine treatment, many investigators have concluded that amphetamine use does not increase a patient's likelihood of later developing SUD, and that it may actually exert a protective effect against substance abuse later in life based on population-level studies - that is, some have concluded that stimulant-based treatment of ADHD early in life may decrease drug abuse later in life. For instance, Barkley and colleagues, the same group whose results indicated a significant increase in cocaine use amongst ADHD patients treated with stimulants, still concluded that treatment of ADHD had no effect on the likelihood of using a number of drugs<sup>19</sup>. A similar study that followed 56 medicated and 19 unmedicated patients found that there was no association between treatment and drug abuse<sup>27</sup>. A study that followed 285 treated and 84 untreated ADHD patients also concluded that SUD did not develop as a result of stimulant treatment<sup>28</sup>. A meta-analysis of several studies also found that for any category of drug use, stimulant treatment decreased the risk that an individual would abuse drugs in general<sup>29</sup>. Review papers on the subject of SUD and its relationship with ADHD have also come to the conclusion that childhood treatment with stimulants is negatively correlated with substance abuse<sup>17,30</sup>.

### **Limitations of Studies that Suggest a Negative Correlation Between Amphetamine Treatment and Drug Abuse**

Although many studies conclude that stimulant treatment is protective against the development of SUD when prescribed to ADHD patients, the validity of these studies is questionable. For instance, many of the studies that come to this conclusion are

funded in full or in part by drug companies such as Pfizer or Eli Lilly, which manufacture ADHD medications<sup>2,9,19,22,27,29</sup>. These studies have clear financial biases in terms of their conclusions. Reviews and meta-analyses are particularly dubious when a conflicting financial interest exists, because they may select papers that suggest a desired result.

In addition, studies with larger sample sizes and meta-analyses tend to group all types of substance abuse into one category, or simply distinguish between "drug abuse" and "alcohol/tobacco use" categories<sup>28,29</sup>. Large bins of categorization produce a confounding variable, because stimulant drugs are known to reinforce and prime other stimulant drugs most reliably<sup>31</sup>. The fact that amphetamine treatment has been suggested to protect against or have no correlation with the use of depressants such as marijuana or alcohol makes placing all drugs of abuse into one category especially problematic<sup>25</sup>. The decreased risk factor for depressant use and the increased risk factor for stimulant use interfere with each other when considered together, thus concealing any specific trends that might exist.

Of two predominant studies that separated "substance abuse" into individual drugs or drug subcategories, one study found a significant increase in cocaine use, while the other found no significant increase<sup>19</sup>. However, the latter study had a small sample size of 56 medicated ADHD patients and 19 non-medicated patients<sup>27</sup>. It is possible that if larger sample sizes were obtained, a significant increase would have become apparent. This conclusion seems increasingly likely since the prevalence of stimulant abuse in society is generally not as high as for other drugs such as cannabis<sup>33</sup> or alcohol, especially amongst ADHD patients in general<sup>9,10,32,33</sup>. Therefore, a much larger sample size is needed to compare stimulant-specific abuse amongst ADHD patients.

Furthermore, if treatment with stimulants does in fact exert a protective effect against general drug abuse and not illicit stimulant abuse, the analysis of drug abuse in general as a single category would actually downplay the increase in stimulant abuse amongst patients. Untreated subjects would be much more likely than treated subjects to participate in non-stimulant abuse, confounding a large portion of studies.

Based on the idea that those with a later onset of treatment have a higher potential for stimulant abuse, it is probable that if the age of treatment onset were compared, patients with a later onset of treatment would show a specific increase in illicit stimulant abuse in adolescence and possibly into adulthood. However, those treated at a younger age may not have a statistically higher percentage of abuse of any drug. If it is true that subjects treated earlier are less likely to abuse stimulants than those treated later in adolescence, any study that does not compare age of onset and likelihood to develop stimulant-specific abuse possesses a significant weakness. Most of the studies that come to the conclusion of a negative correlation between amphetamine treatment and substance abuse fail to accurately assess age of treatment onset when evaluating data, thus mixing information from individuals that may have a

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higher risk of drug dependence with those that may have a lower risk of drug dependence because of age of treatment onset.

Finally, none of these studies take into account the differences between methylphenidate and amphetamine. Since amphetamine has been shown to have an increased potential for abuse compared to methylphenidate and other ADHD medications, these studies therefore downplay the exposure to risk of substance dependence that is put forth with amphetamine prescription.<sup>11</sup> The majority of population studies that have concluded that stimulant-based treatment has no effect on the development of substance abuse later in life fail to take into account all of the factors necessary to produce accurate correlations.

## Discussion

Current knowledge regarding the effects of amphetamines on stimulant-specific abuse in animals and general drug abuse in humans is not consistent. Studies on animal models have concluded that amphetamines specifically raise the tendency to self-administer stimulants, such as cocaine and nicotine, largely due to the sensitization of the rewarding effects of amphetamine that results in drug-seeking behavior. Some population-level studies on patients have been able to confirm this hypothesis. On the other hand, other population-level studies based on surveys and meta-analyses have concluded that stimulant prescription has no correlation with the development of substance abuse. These studies, however, all possess one or more of the following flaws: failing to distinguish between stimulants and depressants in terms of drugs abused by patients; failing to distinguish between amphetamine medication and other stimulant treatment; working with sample sizes far too small to accurately reflect the level of dependence that might develop to stimulants, specifically; and failing to consider the age of the patient at treatment onset.

Taken together, evidence suggests that amphetamine treatment of ADHD causes a small increase in potential for stimulant drug abuse and possibly a decreased potential abuse of depressants. The risk for developing stimulant abuse is likely dependent on age of onset of stimulant prescription, with those treated in adolescence and young adulthood at a higher risk. However, there are no conclusive studies to verify this hypothesis. Considering that the amphetamine treatment for ADHD is on the rise, it would be prudent for an independent research group concerned with the health of ADHD patients to conduct a large-scale study that accounts for the variables mentioned above, using a large population of both treated and untreated ADHD patients to test specific dependence of stimulant class drugs that arise from treatment with amphetamines. Another potential method of study might include comparing the number of formerly treated ADHD versus untreated ADHD patients amongst a population known to have abused stimulants, adjusting for the percentage of treated versus untreated ADHD individuals amongst the ADHD population. A conclusive study on this matter would allow parents, schools, and physicians to more accurately consider the treatments

available for children with ADHD.

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