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Misuse of Prescription Stimulants and Their Effect on Cognition

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Abstract

Prescription stimulants like Adderall and Ritalin are increasingly being diverted and misused by college students who fail to recognize the potential health risks in an effort to improve academic performance. The main aim of this literature review is to address the prevalence of their misuse, the effects they have on cognition, and adverse side effects that are typically associated with their use. Despite being frequently referred to as "cognitive enhancers" or "smart pills," results from studies on these medications remain mixed/unclear as to whether cognitive domains such as memory, executive function, and processing speed are actually enhanced. However, not surprisingly, it has been made clear that both individuals with ADHD and individuals without ADHD see some benefit with regard to the cognitive domain of attention when using prescription stimulants. On top of the need for further studies, there is much ethical debate to be had regarding the use of these medications and their presence in academia and society.

Introduction

Caffeine, a substance found in everyday items such as coffee and energy drinks, is one of the oldest and most commonly used stimulants in the world. It, like other stimulants, can impact the consumer's energy and concentration levels while promoting feelings of wakefulness and alertness through manipulation of neurotransmitters and their respective synaptic receptors in the brain. Unlike the hot morning beverage, though, modernly used synthetic stimulants weren't discovered until the early 1900s, where they were put to use in a variety of ways, including weight loss programs, bronchodilation in asthma, promotion of alertness in the military, symptom management in narcolepsy, and emotion control in depression.[1] More recently, however, prescription stimulants have been most commonly recognized as the first-line treatment of attention-deficit/hyperactivity disorder (ADHD). In fact, the labeled indications for the most common prescription stimulants are almost exclusively for the treatment of ADHD.[4,5,6,7,8]

Nowadays, prescription stimulants, like Adderall and Ritalin, are commonly referred to as, "cognitive enhancers" or "smart pills," by much of the general public. While these medications require a prescription from a healthcare provider regarding a medical diagnosis such as ADHD, they are frequently misused based on the widespread belief that they enhance performance. This has led to a steady increase in the rate of prescription stimulant misuse over the past several decades and therefore deserves to be investigated due to potential public health concerns.

Although prescription stimulants have proven to be successful in treating the symptoms of ADHD, it remains unclear whether they convey an equal benefit to non-ADHD individuals. Thus, the purpose of this paper is to answer the question: Do prescription stimulants enhance cognition in individuals not diagnosed with ADHD? In addition to answering this primary

question, other issues surrounding these medications, specifically related to the prevalence of their misuse and adverse side effects typically associated with their use, will also be explored. Following a background presenting the currently known research regarding prescription stimulants will be a discussion of potential ethical implications that are connected to their use.

Granted the extensive pattern of prescription stimulant misuse, beliefs regarding their performance enhancing capabilities, and their success in treating ADHD, it is hypothesized that these medications do in fact hold some potential for cognitive enhancement in individuals not diagnosed with ADHD. However, the scope of the level of enhancement is predicted to be minimal and have a primary effect on the cognitive domain of attention.

Background

ADHD and Prescription Stimulants

Before we can determine the effects of prescription stimulants on non-ADHD individuals, it is first important to understand the condition for which these medications are commonly used along with some key features of the medications themselves. Therefore, this first section aims to describe the prevalence and pathogenesis behind ADHD, while including names and characteristics of several common prescription stimulants.

ADHD, characterized by the DSM-5 as a persistent pattern of inattention and/or hyperactivity-impulsivity, is one of the most frequently diagnosed neuropsychiatric disorders in children and adolescents.[2] ADHD is most commonly seen in young boys and has been reported to carry a prevalence of 10 percent amongst children aged 4-17 in the U.S.[3] The condition frequently comes to parents' and clinicians' attention when children present with poor grades in school due to persistent distractions and patterns of misbehavior.

Although ADHD is historically a condition of youth and was previously thought to diminish with age, it has become recognized as a condition that carries on into adulthood. In fact, many epidemiologic studies estimate a prevalence of 4.4 percent in the U.S. and 3.4 percent globally in individuals aged 18-44.[2] Similar to the impact ADHD has on the education of children and adolescents, ADHD in adulthood can confer remarkable disability, especially in occupational and academic settings. Thus, it is important to accurately recognize and manage the symptoms of ADHD in all age groups.

The diagnostic criteria that must be acknowledged before arriving at the diagnosis of ADHD is the same in both children and adults.[2] One unique difference, however, is that children under the age of 17 years old require ≥6 symptoms of inattention or hyperactivity-impulsivity to be present, whereas adults over the age of 17 years old require ≥5 or more symptoms.[2] Some symptoms of inattention include difficulty sustaining tasks, reluctance to participate in tasks that demand persistent mental effort, and being easily distracted by unrelated stimuli. Concerning hyperactivity-impulsivity, symptoms include frequent fidgeting, excessive talking, and frequent interruptions or intrusion on others.[2] On top of expressing the required symptoms, other key features demand that the symptoms must interfere with daily functioning and have persisted for at least the last 6 months.[2]

Moving forward, it's essential to mention the mechanism that propels the symptoms previously discussed along with the medications that control them. While the pathogenesis of ADHD isn't entirely understood, it is widely believed that a genetic imbalance of catecholamine metabolism in the prefrontal cortex, particularly of the catecholamines dopamine and norepinephrine, plays an important role.[3] This imbalance results in the neuropsychological deficits related to executive function that are seen in individuals with ADHD such as inhibited

memory and verbal learning, slowed information processing, lack of vigilance, and reduced attention span.[2] An increase in catecholamine metabolism therefore explains the widespread use of stimulants in management of ADHD, which serve to counter the decreased levels of dopamine and norepinephrine in the brain. Prescription stimulants include a long list of different medications, but the most common ones fall under these two main categories: "amphetamine products" and "methylphenidate products."

Dextroamphetamine-Amphetamine, commonly known by its brand name Adderall, Dextroamphetamine, branded Dexedrine, and Lisdexamfetamine, or more well-known as Vyvanse, are three amphetamine stimulants commonly used in the treatment of ADHD. Each of these medications is classified by the Drug Enforcement Agency as a C-II controlled substance, meaning that although they serve a medical purpose, they have a high potential for abuse and dependence.[4,5,6] With the exception of Vyvanse, they come in both short and long-acting versions, which can vary in onset of action time from <1 hour to 2 hours and can maintain effect from 4-16 hours after administration.[9] Because both Adderall and Dexedrine are sympathomimetic amines, they share a common mechanism of action that causes the release of catecholamines (specifically dopamine and norepinephrine) from their storage sites in presynaptic nerve terminals.[4,5] Perhaps less significantly, but nonetheless an important aspect of their function, they also have the potential to block the reuptake of catecholamines via competitive inhibition.[4,5] Comparatively, Vyvanse is a prodrug that eventually converts into dextroamphetamine, where it then acts similarly to the other two medications by increasing the amount of synaptic dopamine and norepinephrine.[6]

Methylphenidate, typically recognized as Ritalin or Concerta, and dexmethylphenidate, branded Focalin, fall into the other subcategory of CNS stimulants that is frequently used in the

management of ADHD. Similar to amphetamines, these medications are C-II controlled substances and require close monitoring.[7,8] Both of these medications come in short and long-acting versions, with a typical range of onset of action between 0.5 and 2 hours and a duration of effect lasting from 3 to 12 hours after administration.[9] Focalin is known to be more potent than Ritalin because it both releases dopamine and norepinephrine into the extra neuronal space and blocks their reuptake, whereas Ritalin only inhibits their reuptake.[7,8]

With regards to efficacy of these two categories of prescription stimulants in the treatment of ADHD, a 2018 meta-analysis of 51 drug trials revealed a higher reduction of symptoms in patients prescribed with amphetamines when compared to others who were prescribed methylphenidate.[10] However, despite being inferior to amphetamines in reducing symptoms in patients diagnosed with ADHD, methylphenidate and dexmethylphenidate maintain an overall higher safety profile.[10] This is likely due to the fact that amphetamine products have a stronger effect on dopamine and norepinephrine than methylphenidate products.

In sum, ADHD has a relatively high prevalence rate in the U.S. and may see some growth due to increasing acceptance that the condition can occur amongst all age groups. The DSM-5, a product of the American Psychiatric Association, has repeatedly been updated and should be referenced when considering a diagnosis of ADHD. The symptoms included in the psychiatric manual are widely believed to be a result of increased metabolism of dopamine and norepinephrine and are therefore best treated with prescription stimulants, such as Adderall and Ritalin, which serve to create a normal balance of synaptic catecholamines.

Diversion and Misuse of Stimulants

Now that we know more about common prescription stimulants and the condition for which their use is indicated, let's discuss some of the reasons for which their use is not indicated.

This section will review the prevalence of misuse of prescription stimulants, who is misusing these medications, risk factors leading up to misuse, how the drugs are acquired, and motivations for misuse.

To start, it's important to clarify what exactly misuse means. The National Survey on Drug Use and Health defines misuse as use of a prescription medication in any way not directed by a doctor, which includes but is not limited to, using without one's own prescription, using in greater amounts and/or frequencies, use to get high, and selling or sharing with others.[11] Conversely, prescription use is defined as the utilization of a prescription medication in the manner instructed by the prescribing physician.

As mentioned earlier, prescription stimulants are categorized by the Drug Enforcement Agency as C-II controlled substances. Meaning that, despite their positive effect on treating certain medical conditions, they run a high risk for misuse that can lead to addiction and dependence, amongst other consequences, as a result of their actions on the reward center of the brain.[11] Shockingly, some laboratory studies have revealed that animals, when given the opportunity, will repeatedly dispense methylphenidate, similarly to how they would with cocaine, due to its euphoric effect when taken in higher doses.[13] So, like many other C-II drugs, such as opioid analgesics and benzodiazepines, stimulants have found a place in the black market to be used and sold illicitly.

The rate of stimulant prescriptions for the treatment of ADHD has steadily increased over the past few decades. In fact, the rate of prescriptions more than doubled from 0.6 percent in the late 1980's to 2.7 percent in 1997.[12] A more recent study that was conducted in 2016 revealed past-year prescription rates as high as 6.4 percent in the United States.[11] This increase in prescriptions is thought to be mostly due to advances in psychiatric diagnostic practices and an

overall increase in duration of treatment of ADHD that extends well into adulthood.[13,14] These findings are important because the increase in prescription rates is directly related to the increased rate of misuse due to a resulting widespread availability and diversion of these medications. In 2000, prescription stimulant misuse, specifically regarding methylphenidate, was reported to have a past-year prevalence of 1.2 percent.[14] A later investigation unveiled a 67 percent increase in the misuse of prescription stimulants between 2006 and 2011 that was accompanied by a roughly 156 percent increase in emergency room visits related to misuse.[12] Most recently, a 2016 study found an overall past-year prevalence of misuse to be 2.1 percent of the general population in the United States.[11]

There is a wide variety of types of people who misuse prescription stimulants, from athletes and the general public, to college students and even individuals diagnosed with ADHD who hold a valid prescription. The vast majority of research, however, has identified undergraduate college students as the primary group when it comes to misuse, specifically individuals aged 18-25.[11,12,13,14] In fact, studies have shown that nonmedical use of prescription stimulants is the second most common form of illicit drug use amongst college students, following marijuana.[13,14] One study quoted a college student stating, "getting Adderall and Ritalin is probably easier than getting alcohol on this campus."[13] A survey conducted in 2003 of a random sample of 9,161 undergraduate students attending a public university in the U.S. reported a rate of illicit use of 8.1 percent.[13] Interestingly, this number was higher than individuals who reported prescription use related to a diagnosis of ADHD.[13] Ultimately, most studies appear to indicate an overall prevalence of prescription stimulant misuse in the range of 5 to 6 percent amongst traditionally aged college students.[11]

The frequency at which college students misuse prescription stimulants is another important matter. A 2002 study found that out of a 35.3 percent past-year prevalence rate, 10 percent used monthly and 8 percent used weekly.[19] To break it down further, a 2006 study showed 15.5 percent using 2-3 times per week and 33.9 percent using 2-3 times per month.[19] Other studies showed more rates of irregular use of prescription stimulants with 40 percent only using once or twice in a lifetime, which were reported to be due to particularly stressful times related to academic pressures.[19]

Although undergraduate students have been the focus of most of the studies on the misuse of prescription stimulants, graduate students have begun to receive an increasing amount of attention. Several studies conducted over the past two decades have directed the spotlight on health professional students, some of which include medical students, pharmacy students, and dental hygiene students. Separate studies revealed that over 10 percent of medical students, 7 percent of pharmacy students, and 12.4 percent of dental hygiene students reported misusing prescription stimulants.[14] Another study of overall graduate students reported a lifetime prevalence of nearly 17.5 percent. [12]

Risk factors that make an individual more susceptible to misusing prescription stimulants include attending college, male gender, white race, age 18-25, affiliation with a fraternity, lower grade point average, living in off-campus housing, previous exposure, and having a history of substance abuse. [13,14] Curiously, individuals who were initiated on prescription stimulants for the management of ADHD during high school or college were three to seven times more likely to report illicit use than individuals who were never prescribed stimulants.[13] Conversely, students initiated on stimulant medication for treatment of ADHD during elementary school reported a

lower probability of illicitly using their medication when compared to individuals who were never prescribed stimulants.[13]

The majority of nonprescription stimulant users stated they acquired the medications from friends and peers, while only a few received them from family members.[13,14] Notably, less than 1 percent of students mentioned obtaining prescription stimulants from a dealer.[13] A 2008 study found that lifetime rates of diversion ranged from 16 to 29 percent, while another study found 54 percent of college students with valid prescriptions for stimulants had been solicited to divert their medication. [13,14] Another study demonstrated that due to widespread popularity of these medications, roughly 29 percent of 334 participating college students sold or gave their prescription stimulants to others. [14]

Studies consistently indicate the main motivation for misusing prescription stimulants amongst college students is cognitive and academic enhancement. A 2011 study on medical and health profession students found that 93.5 percent of students who were misusing prescription stimulants stated their objective was to increase focus and concentration on studying.[14] This is particularly notable at the end of a school semester when students find themselves under immense academic stress and often resort to taking these drugs to study through the night and complete projects.[14] Other less reported reasons for taking prescription stimulants include weight loss, curiosity, coping with stress, staying awake, and recreational use to get high.[12,14] Recreationally using prescription stimulants to get high is of particular concern due to a sequentially higher dose to produce the desired euphoric response, which poses a higher risk for adverse health effects.

In closing, this section has identified an increasing prevalence of not only prescription stimulant misuse, but also medically indicated prescription use. It is likely that increases in both

of these areas is directly related, where the increase in prescription use has led to the increase in prescription misuse by way of medication diversion. Although college undergraduate students are the primary misusers of prescription stimulants, studies have identified graduate students as a second group with high rates of misuse. These groups appear to be misusing prescription stimulants primarily in an effort to enhance their academic performance and have likely contributed to the prominence of nicknames such as "smart pills" when referring to commonly used prescription stimulant medications.

Cognition and Cognitive Assessments

Being that cognitive and academic enhancement is consistently reported to be the main motivation behind misusing prescription stimulants, it's time to take a look at whether or not that is actually achievable. Therefore, the purpose of this section is to put clarity behind the term, cognition, and briefly describe how this term is broken up into individual aspects. Secondly, several commonly used psychological tests that are frequently used in the assessment of cognition will be identified and described.

Simply put, cognition is the mental process by which humans acquire, understand, and interpret knowledge that they are exposed to. Moreover, cognition is broken up into several key domains, which include sensation, perception, motor skills and construction, attention and concentration, memory, executive functioning, processing speed, and language/verbal skills.[21] Although there may be overlap and difficulty in clearly separating each of these interconnected domains, they can be further broken down into unique subcategories (e.g. executive functioning consists of reasoning, problem solving and component skills management), which is helpful in identifying which psychological test to perform when assessing cognition. It's important to note that most current studies addressing the impact of prescription stimulants on cognition did not

assess all of the cognitive domains. Rather, studies selected to assess cognitive areas that were thought to be most relevant to ADHD and academic performance. Specifically, attention/impulsivity, memory, executive function, and processing speed were repeatedly mentioned in a number of studies.

As one might imagine, decades of clinical research have produced a vast number of psychological tests aimed at assessing cognition and each of its individual domains. And, while many of the existing cognitive tests have been utilized in the evaluation of ADHD and the effects of prescription stimulants, four particular tests have been repeatedly used amongst studies. These tests include the continuous performance task, digit span task, Wisconsin card sorting task, and digit symbol substitution task.

Although the continuous performance task (CPT) is primarily used to assess attention/impulsivity, it has also been used in some studies to assess memory and processing speed. CPT can be administered to a subject in a variety of ways, but each format typically consists of requesting the subject to detect simple isolated stimuli while simultaneously being exposed to a separate, constant flow of distractor stimuli.[21] The subject is graded based on a combination of appropriate detections of the isolated stimuli, missed detections (errors of omission), inappropriate detections of the distractor stimuli (errors of commission), and reaction time.[21] This is one of the most commonly used tests in the assessment of ADHD and can be presented at multiple levels of intensity.

The digit span task (DST) assesses memory. This task involves presenting the subject with an increasingly growing sequence of numbers and then requesting the subject to repeat that sequence in the same order, in reverse order, or both.[15,21] This task can vary in the quantity of numbers presented as well as in the timeframe in which the subject is expected to recall the

sequence.[15,21] The subject is graded based on the size of the number sequence they were able to successfully recall.[15]

The Wisconsin card sorting task (WCST) assesses executive functioning, while expressing particular concern for its cognitive flexibility, reasoning, and problem solving aspects.[16,21] The subjects of this assessment are instructed to infer a particular pattern by matching cards based on the test examiner's feedback.[16,21] The cards will each share similarities, but they will not be exact pairs. Success of this task demands that the subject consider new and unique strategies upon failed card matching attempts as indicated by the examiner.[21] The subject is graded based on the amount of errors produced and their ability to learn from their mistakes.

Lastly, the digit symbol substitution task (DSST) assesses processing speed. Subjects of this task are provided with a list of numbers that each correspond to a unique symbol.[16] Upon brief familiarization with the list, a symbol will be revealed to the subject.[16] The subject is then supposed to refer to the list as a key in order to correctly match the symbol with its equivalent number.[16] Granted this task assesses processing speed, the subject is expected to perform as quickly as possible and is graded based on a combination of time used and the amount of correct responses.[16,21]

To summarize this section, cognition was defined and broken up into the individual domains of sensation, perception, motor skills and construction, attention and concentration, memory, executive functioning, processing speed, and language/verbal skills. Per their relationship with the pathophysiology of ADHD, four commonly studied cognitive domains are attention/impulsivity, memory, executive function, and processing speed. While each of these domains is very much connected to the others, several psychological tests exist to isolate and

assess the functioning of each individual one. Respectively, the four emphasized domains are assessed by CPT, DST, WCST, and DSST.

Impact of Prescription Stimulants on Cognition in Individuals with ADHD

This section aims to describe the symptomatic improvements seen by individuals with ADHD who are using prescription stimulants. Importantly, the cognitive baseline held by individuals with ADHD will be addressed, followed by research findings related to the impact of prescription stimulants on specific cognitive domains and their effect on academic performance. Lastly, a dose-response relationship between prescription stimulants and specific cognitive domains in individuals with ADHD will be discussed.

Inherently, individuals diagnosed with ADHD have certain behavioral and cognitive deficits. Specifically, these individuals lack in the areas of selective attention, impulsivity, memory, reaction time, information processing speed, and executive control.[14] Thus, the cognitive baseline held by children and adults with ADHD is said to be lower than individuals not diagnosed with ADHD. For this reason, it is important to recognize that improvements found in individuals with ADHD resulting from the treatment of prescription stimulants is seen through a lens of normalization, rather than one of enhancement.[20,22]

Having acknowledged a lower starting cognitive baseline amongst individuals with ADHD, it is not surprising to reveal that the majority of studies found overall increased rates of cognitive improvements with prescription stimulants, particularly regarding attention, impulsivity, memory, and reaction time.[20,22] Of note, executive function did not see any enhancement. When comparing stimulant use in ADHD to non-ADHD, reports suggest a similar upward trend in some areas of cognition, but that there is far more impact to be had when the

cognitive baseline is already low to begin with. Undoubtedly, it is for this very reason that prescription stimulants continue to be the first-line treatment option for the symptoms of ADHD.

Although students with ADHD appeared to experience more of a positive cognitive effect by using prescription stimulants than did their non-ADHD counterparts, they did not academically outperform them. In fact, studies have shown that even though prescription stimulants may increase their note taking, scores on quizzes, homework completion, and overall academic productivity, individuals with ADHD tend to utilize more remedial academic services, repeat or withdraw from courses, and are less likely to attend college in general.[14] One study comparing grade point averages discovered that college students with ADHD had statistically lower averages than non-ADHD students.[22] Therefore, these results tend to indicate that although academic improvement is seen in students with ADHD who take prescription stimulants, they still seem to achieve less academically than non-ADHD students. This is likely due to unimpacted deficits in the area of executive function, which ultimately helps control other cognitive domains and is key to problem solving.

Interestingly, a study from the late 1970s suggested the dose required to produce the optimal cognitive effects was lower than the dose required for desired behavioral effects.[20] That's to say, a higher dose is required to produce the effects visible to others. Several studies have since shown a dose dependent response to prescription stimulants based on which type of task an individual was asked to perform.[20] For example, individuals with ADHD responded better in the areas of attention and memory when administered higher doses of a stimulant. Whereas, no benefit was observed from receiving a higher dose in areas such as executive functioning and motor speed.[20] Most dose response studies regarding optimal cognitive and behavioral effects of

stimulants have revealed a high level of variability, indicating the importance for patient customization based on specific deficits.[20]

To come to the point, individuals who are diagnosed with ADHD maintain an overall lower cognitive baseline than their non-ADHD counterparts. Recognizing this difference is important when comparing the effects of prescription stimulants between the two groups. Perhaps predictably, the cognitive domains of attention, impulsivity, memory, and reaction time saw the most benefit from taking prescription stimulants. And, although overall academic improvements were reported, individuals with ADHD did not see the same level of academic achievement as non-ADHD individuals. Lastly, a dose-response relationship between prescription stimulants and specific cognitive domains in individuals with ADHD was identified early on and indicates the value of tailoring prescription stimulant doses to the unique deficits of each patient.

Impact of Prescription Stimulants on Cognition in Individuals without ADHD

Opposite to the previous section, the goal here is to identify the effects of prescription stimulants in individuals who have never received a medical diagnosis, and who are therefore misusing these medications. To start, the subjective views of the effects of prescription stimulants held by non-ADHD college students will be mentioned, followed by study results as they relate to the four cognitive domains of interest.

There are numerous anecdotal reports made by college students claiming the cognitive benefits of prescription stimulants. But, as one might infer, many of these claims could very well be the result of the placebo effect. Wherein the student simply believes that he or she had enhanced cognitive abilities due to hearsay regarding the prescription stimulant they consumed. Another possibility is that the student may have improved their quality and quantity of work

simply due to a resulting increase in energy, wakefulness, and motivation that was produced by the prescription stimulant, rather than an enhanced cognitive ability.[19] Responses from a 2014 survey of 18 healthy university students regarding subjective experience of enhancement and objective academic results indicated mixed results.[18] Concerning the subjective experience, one participant stated, "I could focus better and I wasn't distracted," while another highlighted his improved memory by saying, "Usually I have to get things into my short-term memory and then into long-term memory… Under Ritalin it was enough to read over it quickly and I was able to remember it days afterwards…"[18] There were inconsistent answers, however, when it came to actual academic results, where most students reported good results, a few reported complete confidence that the stimulant helped them, and others saw no improvement in their grades.[18] Obviously, the results of this survey indicate a strong pattern of belief in prescription stimulants, but confirms that there is a lack consistency when it comes to actual academic results. Not to mention, academic results could be related to many factors other than the medications, such as a variance in studying styles, time allowed in advance to study, and a difference in overall cognitive baselines.

Putting subjective student reports aside, most studies produced results indicating either minor cognitive enhancements, no enhancement, or mixed/unclear results, with no studies reporting high levels of cognitive enhancement. Predictably, with respect to the domain of attention, there was an overall consensus that individuals not diagnosed with ADHD experienced a minimal to moderate increase when using prescription stimulants.[14,15,17] When assessing participants with CPT, results of three studies indicated a significant decrease in errors of omission, meaning the participants were less distractable.[14,17] Four studies saw decreased reaction times, which is supportive of the participants' concentration.[14,17] And lastly, one study

reported marginally decreased errors of commission, which can be interpreted as a decrease in impulsivity when posed with irrelevant stimuli.[15]

Unlike attention, studies of prescription stimulants on memory appeared to demonstrate higher amounts of mixed/unclear results. Studies from 2002 and 2015 on memory and stimulant use via DST reported a small, yet significant improvement in participants' memory.[12,17,19] This was on par with the results of three earlier studies which, through the implementation of assessments other than DST, also reported slight increases in memory.[14,17] Conversely, though, various other studies using DST indicated that stimulants had no effect on memory.[14,19] Finally, only one study, conducted in 2018, cited a slight impairment in the memory of participants taking a stimulant when compared to the placebo group via DST.[15]

It's important to mention that memory as a cognitive domain is the most complex and broad of the cognitive domains and encompasses many subcategories.[21] Most studies found common ground, though, in focusing on a single form of memory: working memory. Working memory is described as one's ability to maintain and manipulate information for conscious use.[21] In comparison to other long-lasting forms of memory, one literature review describes working memory as an "internal scratch pad" that can be used to "consult and manipulate" when carrying out varied tasks.[19] Perhaps its applicability to academic performance is why many studies chose to concentrate on this form of memory.

Again, in the assessment of executive function, most studies produced mixed/unclear results. Using WCST in 1996 and later in 2003, a study conducted by a group of the same authors concluded that prescription stimulants had no effect on executive function.[14,19] To the contrary, a systematic review that included data from a 2009 study using WCST noted fewer perseverative errors amongst participants using stimulants, meaning participants were able to

successfully deduce patterns and problem solve better than their placebo counterparts.[17] However, a commonly referenced study from 2010 noted an increase in perseverative errors amongst participants who underwent WCST, indicating stimulants result in a decreased cognitive flexability.[12] These results are on par with those mentioned previously regarding individuals with ADHD, where prescription stimulants don't appear to have any impact on executive function.

Lastly, and perhaps the least studied of the four cognitive domains included in this review, is processing speed. Studies targeting this area yielded results indicating an overall positive relationship between prescription stimulants and processing speed, where participants were able to more quickly and accurately match numbers to their equivalent symbols in DSST. The primary study of reference is a 2016 meta-analysis that extracted data from 8 different DSST studies for a total of 345 subjects, revealing a small, but significant improvement in processing speeds amongst participants.[12,16]

In summary, the results of studies showing the effect of prescription stimulants on cognition in individuals not diagnosed with ADHD are fairly mixed and unclear. Although it was not a unanimous decision, and considering the possibility of the placebo effect, the majority of college students misusing these medications are under the impression that they benefited from their use. Academic grades, however, illustrate a mixed story, where not everyone earned the grade they expected as a result of taking prescription stimulants. Furthermore, three out of the four cognitive domains emphasized in this paper expressed variable results that range on the spectrum from positively impacted to unfavorably impacted, while only one domain, attention, exhibited concordant results of a positive impact.

Adverse Effects of Prescription Stimulants

In accordance with increasing amounts of prescription stimulant use, whether it be under the guidance of a physician or not, it is important to review the common adverse effects often associated with their use. While the adverse effects of prescription stimulants may hold some variance, they can usually be predicted based on their mechanism of action in the sympathetic nervous system. The expected side effects of a normally prescribed dose typically include an increase in blood pressure, increased heart rate, increased body temperature, decreased sleep, decreased appetite, and dry mouth.[11] Higher quantities, on the other hand, can result in a dangerous overdose. Signs leading up to an overdose can include mydriasis, tremor, agitation, hyperreflexia, combative behavior, confusion, hallucinations, paranoia, and seizures.[11] And although rare when compared to prescription opioids, death may result from stimulant overdose. In fact, following a one-year increase in mortality of 33 percent in the United States, 2016 saw over 7500 deaths related to prescription stimulant overdose.[11] Out of the population that represents the recent 33 percent increase in mortality, younger males aged 15 to 24 years saw the biggest jump.[11]

Perhaps the most concerning side effects of prescription stimulant use relate to the cardiovascular system. One might presume that persistent elevations in blood pressure and heart rate, especially after prolonged use, would be a direct cause of other conditions such as hypertension, myocardial infarctions, arrhythmias, cardiomyopathies, and sudden death. In fact, a recent study of 125 adult subjects diagnosed with ADHD who were treated with prescription stimulants resulted in persistent elevations in both systolic and diastolic blood pressures ranging from 3 to 5mmHg and was accompanied with an average increase in heart rate of about 5bpm when compared to baselines.[9] These seemingly inherent elevations in cardiovascular vital signs

would almost certainly imply a future need for antihypertensive medications, especially in individuals who were already elevated or borderline hypertensive before starting on prescription stimulants.

In an effort to address the risk of experiencing adverse cardiovascular events while using prescription stimulants, 7 out of 10 large studies included in a 2012 systematic review concluded that there was no association.[23] To break down the demographic targeted by these studies, 7 were based off of ADHD affected children and adolescents with ages ranging from 2 to 24 years and only 3 were based off of ADHD affected adults ranging from 18 years of age and older.[23] Amongst the studies aimed at children, 6 out of the 7 found no association between adverse cardiovascular events and prescription stimulant use, while 2 out of the 3 studies aimed at the adult population did find some level of association.[23] These studies are important and should be referenced when considering the use of prescription stimulants, especially in older individuals who already have naturally higher risks for cardiovascular conditions due to wear and tear.

Similarly, a different review that was also published in 2012 pointed out several cases of cardiac arrhythmias and infarction found in young adults taking prescription stimulants.[14] One case described a 20-year-old male college student who suffered a myocardial infarction following the ingestion of two 15 mg Adderall XR tablets.[14] The same situation occurred in a 15-year old boy who took two 20 mg tablets of Adderall.[14] While it is important to acknowledge such cases, it is also important to note that this review focused specifically on individual instances that were related to doses above the minimum, whereas the previous review focused on large population-based observational studies. Nonetheless, there is definitely a potential for adverse cardiovascular effects, which points to the importance of being properly evaluated for

cardiac symptoms and history prior to induction and followed by regular pulse and blood pressure monitoring throughout use.[9]

A second, more rare concern regarding prescription stimulants is the potential for developing a drug related psychosis. Interestingly, psychosis borders the opposite side of the spectrum when compared to the cognitive enhancing properties that make prescription stimulants so sought after by university students in the first place. Onset of psychosis is believed to be the result of excess dopamine in the neuronal synapses.[14,24] Therefore, one could infer that the risk for developing psychosis is related to taking a higher dose of prescription stimulants. A study from 2019 identified 343 cases of psychosis out of a total of 337,919 participants who used a prescription stimulant.[24] Of those 343 cases, roughly 31 percent were related to methylphenidate and 69 percent were related to amphetamines.[24] This makes sense since dopamine release is 4 times more potent with amphetamines than with methylphenidate, which primarily blocks the reuptake of dopamine.[24]

Lastly, it's important to mention the role of substance abuse disorder and addiction with regards to prescription stimulants. These medications have the ability to produce pleasurable and motivational dopaminergic responses that are key to addiction formation and have the ability to act similarly to illicit drugs such as cocaine and methamphetamine. Although the risk of addiction is not entirely clear, one study from 2006 estimated that roughly 1 in 20 (5 percent) users of prescription stimulants for reasons other than ADHD meet the criteria for dependence.[19] And, among individuals who went through substance use treatment in 2019, 3.4 percent were for prescription stimulant use.[11] Notably, while reports of individuals with ADHD abusing their prescription stimulant medications exist, labelled use does not appear to increase the overall risk of developing a substance abuse disorder.[13] In fact, it has been reported that prescription

stimulants have a protective quality against ensuing substance abuse disorders in ADHD affected individuals.[13] This protective effect is likely a result of controlling impulsive behaviors typically found in ADHD.

In sum, the sympathomimetic impact of prescription stimulants conveys certain cardiovascular side effects on the human body. Specifically, stimulants have been shown to persistently elevate both blood pressure and heart rate over time. This carries important implications with respect to the potential of developing hypertension and heart failure with chronic use. And, while the majority of studies on children and adolescents have concluded there is no association between prescription stimulant use and adverse cardiovascular events, such as myocardial infraction and arrhythmias, cases of sudden death related to their use do exist in the literature. Adults, on the other hand, appear to have a higher overall association with the risk of experiencing adverse events. Therefore, it is essential to be properly evaluated prior to beginning use of prescription stimulants and maintain a good follow-up schedule to monitor vital signs. Lastly, the issue of substance abuse and dependence is of growing importance due to the addictive qualities exhibited by prescription stimulants and their growing rate of use.

Methods

Relevant literature was identified through searches on PubMed and UpToDate using combinations of the following keywords and phrases: “ADHD diagnosis and treatment,” “amphetamine,” “Dextroamphetamine/Amphetamine,” “Adderall,” “Methylphenidate,” “Ritalin,” “illicit stimulant use,” “stimulant effect on cognition,” “neurocognitive effects of Adderall,” “prescription stimulant use for cognitive enhancement,” “adverse effects of prescription stimulants,” “prescription stimulant use amongst college students,” “prescription

stimulant use amongst university students," "prescription stimulant use in academia," "misuse and diversion of prescription stimulants."

An examination of titles and abstracts was conducted to include only pertinent publications. Initially, 36 sources were identified, but many were eventually excluded from the investigation due to lack of available full-length articles. Ultimately, 26 sources were reviewed, analyzed, and included in this investigation.

Discussion

The information presented in the background section confirms that the prevalence of prescription stimulant misuse continues to rise despite persistently mixed results of their efficacy in the realm of cognitive enhancement. While the results of many scientific studies regarding this topic in non-ADHD individuals do appear to indicate a slight positive trend in some areas of cognition, an equivalent number pointed towards a null effect, and a small number of studies indicated a negative effect. This leaves a lot of room for questions and interpretation surrounding this area and certainly indicates the need for further research to produce more definitive results.

One concerning pitfall identified in many studies and reviews is an absence of concordance with regard to a shared cognitive baseline of study participants. Although this aspect may be difficult to gauge, it is arguably the most important factor in determining the effect of prescription stimulants on cognition. One prominent study of ADHD affected individuals stated, "Because we did not do any assessments to confirm the diagnoses, it is reasonable to assume that some unknown proportion of the diagnoses were questionable. Even though we required that all participants provide a prescription for stimulants before they could be accepted into the study, we did not validate their diagnoses."[22] The same authors also acknowledged the possibility that non-ADHD participants could have been diagnosed with

ADHD had they been evaluated. It is likely that this was not the only study to make assumptions of its participants regarding their cognitive baseline. It is important to maintain a certain level of trust in the diagnostic capabilities amongst colleagues, but it is equally important to double-check diagnoses when in doubt, especially when attempting to arrive at conclusions in medical studies.

Furthermore, key terms also lacked common definitions in many of the existing studies regarding this topic. Amongst those are common dosages and frequency of specific prescription stimulants used, prior study habits and personality traits of participants, and the meanings of cognition and specific cognitive domains. Although each of these variables is important to arriving at one conclusion, describing the individual cognitive domains differently makes it particularly difficult to understand what is even being assessed in the first place. As an example, some studies referred to executive function specifically as cognitive flexibility, whereas others referred to cognitive flexibility and executive function as separate domains. And even though most studies were able to narrow down types of memory specifically to "working memory," it wasn't a unanimous definition.

Another important point to mention regarding the methods of most of these studies is that there was a strong lack of consistency when it came to types of assessments performed. Although this literature review attempted to isolate 4 specific psychological tests (CPT, DST, WCST, DSST) and provided a description of how they functioned, more than 20 other tests were identified amongst studies. This leads to a high amount of variability when trying to compare and contrast the results and arrive to an informed conclusion. It is imperative that future studies define which assessments best reveal the effects of prescription stimulants on cognition and stick to a select few rather than implementing a huge variety.

Of the four cognitive domains that were most emphasized in this investigation, attention/impulsivity appeared to receive the most benefit in both ADHD and non-ADHD individuals. This of course is not entirely surprising, seeing that the main purpose of prescription stimulants in medicine is to reduce symptoms of inattention in ADHD. Perhaps, however, enhancement in this area is of particular importance to most students and other individuals both using and misusing prescription stimulants. Afterall, it was reported that the majority of college aged students misusing these medications did so in times of greater academic pressures related to studying for multiple exams and other end of the year projects. Certainly, granted the high amount of overlap and interconnection amongst the domains that ultimately define cognition, one could argue that attention is most related to learning in that it allows the user to spend more time focused on a desired subject and therefore achieve more academic and career goals. Even if other cognitive domains don't see any direct effect from prescription stimulants, wouldn't an increased level of attention over time impact them? For example, even if memory may not be enhanced, meaning that one could memorize more information in a shorter period of time, spending more time by way of increased attention would surely result in one's ability to remember more information.

Despite the fact that there is still no clear answer regarding the overall cognitive enhancing capabilities of prescription stimulants, it is likely that they will continue to be misused. Therefore, it is crucial to address the multiple ethical concerns surrounding their use. Specifically, what is the role of the healthcare professional in prescribing and managing these medications? Do the benefits of prescription stimulant use outweigh the risks? How should they be treated within academia? Where do these medications fall in the eyes of society? The answers

to these questions are very complex and undoubtedly require the viewpoint from a variety of different angles.

The typical healthcare professional with prescriptive authority will inevitably find themself in a position where they are considering prescribing a stimulant medication such as Adderall or Ritalin. This may happen upon arriving at the diagnosis of ADHD in a young child who has expressed an inability to pay attention in class and whose grades are suffering as a result. Perhaps a stressful appearing young college student is seeing his primary care provider for the first time in years expressing similar symptoms of inattention and impulsivity. Or maybe the provider is approached by a healthy patient who openly states that they just want a prescription for Adderall because they heard it has cognitive benefits. Regardless of the situation, it's up to the discretion of the provider to decide on how to move forward.

A 2013 article quoted the American Academy of Neurology (AAN) saying, "prescribing medications for cognitive enhancement is not ethically obligatory or prohibited, and is therefore ethically permissible, but that refusing to prescribe is also ethically and legally permissible."[25] Notably, though, the AAN followed this by also emphasizing the importance of evidence-based medicine when prescribing stimulants for off-label use.[25] Although helpful, this leaves little official guidance for healthcare professionals and is merely suggestive of two possibilities. The first, and most obvious, is to be a careful and thoughtful diagnostician in order to properly arrive at an evidence-based conclusion before writing a prescription for stimulant medications. The second possibility, while not mutually exclusive from the first, points more towards a dynamic of trust between the healthcare professional and the patient, where the prescriber must believe the patient will safely use, and most importantly, benefit from taking the prescription stimulant, regardless of a diagnosis.

As mentioned earlier, the current data (excluding the domain of attention) remains unclear as to whether a healthy individual would actually benefit from prescription stimulants. Obviously, this would imply that when referencing evidence-based medicine, the healthcare professional should refrain from writing a prescription. However, let's say for example that the healthy patient specifically states he or she would like to be prescribed a stimulant specifically to enhance attention. Granted that attention is the only domain with unanimous support of enhancement, should this patient receive a prescription? One could argue that since attention has proven to be enhanced by use of prescription stimulants that the patient might be a good candidate for its off-label use, of course allowing that the prescriber expresses no concern that the patient is at risk for any adverse drug effects. It could be further argued that increased attention would convey more academic, professional, and economic success, leading the patient to be able to afford a healthier lifestyle that might otherwise be limited. On the other hand, deciphering the intentions of a patient and gaining a high level of trust could prove to be a very difficult task, especially in a world where malingering is commonplace.

Furthermore, the healthcare professional would certainly have to weigh the risks of adverse effects that are associated with prescription stimulant use. Despite being a generally safe medication when used under the guidance of a healthcare professional, prescription stimulants have shown to carry certain risks, especially related to the cardiovascular system. And although the majority of studies mentioned in this review have concluded that there is no increased risk of adverse cardiovascular events associated with prescription stimulant use, it was not arrived at unanimously. Afterall, the FDA has committed a black box warning to several commonly prescribed stimulants for risk of sudden death, which, in spite of being relatively rare, should not be taken lightly and need to be strongly considered before prescribing a stimulant medication. It

might also be hard to believe that a medication associated with persistent elevations in heart rate and blood pressure doesn't translate to future use of antihypertensive drugs. For this reason, it is also important to consider what the future holds for a patient who chronically uses these medications.

Concerns of addiction and dependence are another concern when it comes to prescription stimulants. Based on their classification as C-II controlled substances, it is clear that prescription stimulants pose a threat to developing addictive behaviors. Arguably, though, more studies need to be conducted surrounding the addictive properties of these medications. Nonetheless, it is crucial that healthcare professionals take an in-depth look into each individual patient's substance use history prior to initiating any treatment involving stimulant medications.

Falling outside the court of medical professionals lies a more societal view of prescription stimulants as it pertains to their potential to be used as cognitive enhancers. Granted the steady surge in both use and misuse, it's not surprising that prescription stimulants have been reported on by several media sources.[14] Perhaps what is surprising, though, is the language of approval that is used by many major media outlets.[14] In acknowledging these reports, one study mentioned that 95% of articles in the media indicated at least one possible benefit of using prescription stimulants as "neuroenhancers," while only 58% noted the associated risks and side effects.[14] Obviously, publishing information in such a one-sided manner could be described as irresponsible, but it does not diminish the fact that the public opinion appears to be in favor of at least exploring the idea.

Conversely to what media sources might say, the world of academia appears to be taking a different approach to the issue. For example, in 2012 Duke University implemented a policy that explicitly prohibits the unauthorized use of prescription medication for the purpose of

enhancing academic performance.[14] In fact, the university added this new policy under the category labeled "cheating."[14] Interestingly, the study pointing out this change made the point that by virtue of labeling a policy in such a manner, it is assumed that prescription stimulants do indeed enhance academic performance, thus perpetuating an idea that isn't entirely backed by science.[14]

Academic policies such as this one raise yet another important question: Should the use of prescription stimulants for the purpose of cognitive enhancement be compared to steroid use amongst athletes? This concept definitely has room for debate in all aspects of society, and, upon recognizing the dangers associated with these medications, should be a view through a scope of fairness and equal opportunity. The AAN argues that if given a more accessible place in society, prescription stimulants would undoubtedly be viewed as elective medications by insurance companies and consequently not be covered.[25] The resulting situation would then concern affordability, meaning that only a few members of society would be able to afford their use, thus creating yet another disadvantage for the more marginalized members of society.[25] In an effort to acknowledge the present racial tensions in the United States and the potential disparities that could arise as a result of societal acceptance regarding these medications, one study stated, "cognitive enhancing drugs are not necessarily just the "white" version of cheating... But if "whiteness" serves as a proxy or synonym for a more broadly "privileged" class of student, then cognitive enhancing drugs are indeed seen by some as a tool for academic advancement more often wielded by the privileged."[26]

In closing, this discussion section identified several pitfalls that weakened many current studies while emphasizing the importance of using concordant terminology, psychological assessments, cognitive baselines, and confirming either the presence or absence of a diagnosis of

ADHD in participants. Furthermore, in acknowledging the likelihood that prescription stimulants will continue to be misused, several ethical questions were addressed regarding the role of healthcare professionals as medication gatekeepers, a comparison of the risks versus benefits of prescription stimulant use, and their presence in academia and society. In the end, it is crucial that debate and research surrounding this topic continue to advance in order to arrive at more conclusive answers.

Conclusion

The goal of this literature review has been to investigate and blend together the current research surrounding the misuse and potential cognitive benefits of prescription stimulants. In doing so, it was made clear that the misuse of prescription stimulants has been on the rise due to a widespread belief that they convey certain cognitive enhancing properties. Misuse was noted to be of particular prominence amongst college students, who tend to use them to improve academic performance, especially when faced with stress related to increased workloads. However, despite popular belief, there has yet to be a unanimous consensus amongst studies showing a definitive correlation between prescription stimulant use and enhanced cognition. While nearly all studies resulted in mild to moderate enhancement of attention, results regarding other cognitive domains such as memory, executive function, and processing speed were highly mixed. Public health concerns arise when considering these increasing rates of misuse in spite of unclear results surrounding the efficacy of prescription stimulants and it becomes all the more important to further investigate the matter. It is then essential that future studies implement shared definitions of key terms, identify standard cognitive baselines, and selectively perform standardized assessments.

Ethical debates comparing the use of prescription stimulants to doping and cheating is also worth mentioning. Not only are there certain dangers associated with the use of these medications, but questions of fairness and their potential for increasing the inequality gap is certainly important and the public view on this matter needs be explored. Perhaps the most important ethical consideration pertains to college students, being that misuse is primarily motivated by academic advancement. Students posed with misusing prescription stimulants must acknowledge a handful of considerations, such as their university's academic policy, legal consequences, their potential to self-motivate without the use of a substance in the future, and their own moral code.

Lastly, the current research and ethical debate was followed up with a discussion regarding the role and responsibility healthcare professionals hold with these medications. Obviously, healthcare professionals are the gatekeepers to all prescription drugs. It is therefore immensely important to use good diagnostic and judgement skills in identifying true ADHD patients while also taking into consideration what potential benefits, if any, a healthy, non-ADHD patient might see from using prescription stimulants. In these considerations, it is clearly important that the prescriber appraise the patient's history for substance abuse disorders and weigh the risks of potential adverse effects that could occur while using prescription stimulants.

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