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Prescription Stimulant Medication Misuse: Where Are We and Where Do We Go from Here?

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Abstract

Prescription stimulants, including methylphenidate (e.g., Ritalin) and amphetamine compounds (e.g., dextroamphetamine; Adderall), have been approved by the U.S. Food and Drug Administration for the treatment of attention deficit hyperactivity disorder (ADHD) and are classified by the United States Drug Enforcement Administration (DEA) as Schedule II medications due to their high potential for abuse and dependence (DEA, U.S. Department of Justice, 2015). Despite the potential health and judicial consequences, misuse of prescription stimulants, typically defined as taking stimulants without a valid prescription, or use of stimulants other than as prescribed, has become a serious problem in the United States and abroad, especially on college campuses. The purpose of the present paper is to review historical information concerning prescription stimulants and to summarize the literature with respect to misuse among adults, particularly college students, including risk factors, mediators and moderators, and motivations for prescription stimulant misuse. In addition, evidence is presented concerning the question of whether prescription stimulants truly enhance cognitive functioning in individuals with and without ADHD, and the ethical and professional implications of these findings are explored.

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Lastly, recommendations for addressing prescription stimulant misuse and suggestions for future research are advanced.

Keywords

Prescription stimulant misuse; neurocognitive enhancement; Adderall

The U.S. Food and Drug Administration has approved several types of prescription stimulants for the treatment of attention deficit hyperactivity disorder (ADHD) in children, adolescents, and adults, and the most commonly prescribed stimulants include methylphenidate (e.g., Ritalin) and amphetamine compounds (e.g., dextroamphetamine; Adderall) (Meijer, Faber, van den Ban, & Tobi, 2009). These medications are available in short, intermediate, and longer-acting (i.e., sustained release) forms and a plethora of studies attest to the effectiveness of prescription stimulants in helping to manage the symptoms of ADHD (e.g., Greenhill, Pliszka, & Dulcan, 2002; Fredriksen, Halmoy, Faraone, & Haavik, 2013). The effectiveness of stimulants at improving symptoms associated with ADHD was discovered in 1937 by psychiatrist Charles Bradley who administered Benzedrine sulfate, an amphetamine, to children at the Emma Pendleton Bradley Home in Providence, Rhode Island. Bradley discovered that the children demonstrated improvements in behavior as well as school performance (Bradley, 1937). An increase in the use of prescription stimulants for the management of attention and behavioral symptoms did not emerge until nearly 20 years later when the American Psychiatric Association (i.e., Diagnostic and Statistical Manual) focused on childhood hyperactivity symptoms. Since that time, prescription rates for prescription stimulants have steadily and substantially increased. For example, Zuvekas and Vitiello (2012) reported that during the 1990s, the rate of stimulant prescription use among youth increased significantly, from 0.6 percent in 1987 to 2.7 percent in 1997, with the rate stabilizing around 2.9 percent in 2002. Currently, Iceland, closely followed by the United States, has the highest per capita consumption of methylphenidate in the world among children, adolescents, and adults, while the United States ranks at the top with regard to amphetamine prescriptions (Kaye & Darke, 2012).

Stimulants are believed to exert their effects by targeting the dopaminergic and noradrenergic systems and increasing concentration of these neurotransmitters in the synaptic cleft (Volkow, Fowler, & Wang, 2002). When used as prescribed, prescription stimulants do not pose significant health risks to individuals (Findling & Dogin, 1998). Side effects of prescription stimulants are dose-dependent (Solanto, 2001), and the most commonly reported side effects are decreased appetite, weight loss, headache, insomnia, abdominal pain, dizziness, nervousness, emotional lability, and dry mouth (Weyandt et al., 2014). More severe side effects, including psychosis, seizures, and cardiac events such as tachycardia, hypertension, myocardial infarction, and sudden death are rarely reported in individuals taking therapeutic doses of the medications orally (Greenhill et al. 2002; Graham & Coghill 2008). A number of adverse events, however, have been reported when these drugs are misused (Greydanus, 2015). Serious potential risks associated with excessive dose include, but are not limited to, cardiovascular failure, irregular heartbeat, high blood pressure and paranoia (Volkow, 2005). Route of administration also affects the potential adverse

effects. Using the drugs intravenously or intranasally (i.e., snorting) significantly enhances the potential risks of prescription stimulants (Teter et al., 2006). Furthermore, long-term exposure to high doses of prescription stimulants could increase the risk of adverse cardiovascular effects; however, studies in children and young adults were found to be underpowered to detect such an increased risk (Westover & Halm, 2012). Prescription stimulants are classified by the DEA as Schedule II medications (along with codeine, morphine, and oxycontin) due to their high potential for abuse that may produce psychological and/or physiological dependence (Drug Enforcement Administration, U.S. Department of Justice, 2015). Consequently, prescription stimulants are considered a controlled substance by federal and state law and are subject to criminal charges.

Despite the potential health and judicial consequences, misuse of prescription stimulants has become a serious problem, particularly on college campuses in the United States and abroad (Benson, Flory, Humphreys, & Lee, 2015; DeSantis, Noar, & Webb, 2010; DuPont, Coleman, Bucher, & Wilford, 2008; Dussault & Weyandt, 2013; Hall, Irwin, Bowman, Frankenberger, & Jewett, 2005; Janusis & Weyandt, 2010; Judson & Langdon, 2009; Low & Gendaszek, 2002; Messina et al., 2014; McCabe, Knight, Teter, & Wechsler, 2005; McCabe, West, Teter, & Boyd, 2014; Rabiner et al., 2009; Sharp & Rosen, 2007; Verdi, Weyandt, & Zavras, 2014; Weyandt et al., 2009; White, Becker-Blease & Grace-Bishop, 2006; Weyandt et al., 2013). Misuse of prescription stimulant medication also occurs in the general population, although perhaps to a somewhat lesser extent; for example, Novak, Kroutil, Williams, and Van Brunt (2007) reported an overall prevalence rate of 2% among individuals ages 18–49. Recently, Austic (2015) reported that the peak ages for beginning misuse of prescription stimulants was between 16 and 19 years, with 0.7% to 0.8% of young people reporting nonmedical use of stimulants for the first time in the past twelve months. An important distinction is that misuse, typically defined as taking stimulants without a valid prescription, or use of stimulants other than as prescribed (Babcock & Byrne, 2000; Benson et al., 2015; Weyandt et al., 2013) is an illegal activity and differs from substance abuse disorders (i.e., use of one or more substances leads to clinically significant impairment or distress) (APA, DSM V, 2013).

The purpose of the present paper is to review and summarize the literature with respect to information concerning misuse among adults, including risk factors, mediators and moderators, and motivations for misuse. In addition, information is presented concerning whether prescription stimulants truly enhance cognitive functioning and the ethical and professional implications of these findings. Lastly, unanswered questions concerning prescription stimulant misuse are explored and suggestions for future research are advanced.

Current Use and Misuse of Prescription Stimulants

Prescription stimulants are widely regarded as safe and efficacious for reducing symptoms of inattention, impulsivity, and hyperactivity in the treatment of ADHD (Adler, Spencer, McGough, Jiang, & Muniz, 2009; Adler et al., 2013; Brams, Giblin, Gasior, Gao, & Wigal, 2011; DuPaul et al., 2012; Faraone, Spencer, Aleardi, Pagano, & Biederman, 2004; Retz et al., 2012; Spencer, Adler, Weisler, & Youcha, 2008) and are commonly recommended as part of an individualized treatment regimen for children, adolescents, and adults with the

disorder, including college students (Kooij et al., 2010; National Institute for Health and Clinical Excellence, 2009).

Stimulant Misuse among College Students

Unfortunately, as increasing numbers of individuals with ADHD attend college (Weyandt & DuPaul, 2013), a recent meta-analysis and systematic review have substantiated the availability, use, and misuse of prescription stimulants has risen sharply among college students without the disorder (Benson et al., 2015; Weyandt et al., 2013). Beyond the college demographic, a recent investigation conducted by Chen and colleagues (2016) revealed that misuse of prescription stimulants among adults from the general population increased by approximately 67%, and emergency room visits rose by approximately 156% between the years of 2006 and 2011. Regarding prevalence rates, one of the first studies examining stimulant misuse behavior among college students (Babcock & Byrne, 2000) revealed that 16.6% of the students sampled reported having engaged in prescription stimulant misuse behavior, while other studies have indicated prevalence rates as high as 43% (DeSantis, Webb, & Noar, 2008). More recent research reported the prevalence rate of stimulant misuse was estimated to range between 13 – 23%, approximating around 17% on average (Benson et al., 2015). Studies consistently indicate that the main motivation college students report for misusing prescription stimulants is cognitive and academic enhancement (Benson et al., 2015; Rabiner et al., 2009; Weyandt, et al. 2013). Interestingly, misuse of these medications appears to be *negatively* associated with academic performance, indicating that misuse may not necessarily lead to academic enhancement, despite students' perceptions of their benefits. According to Weyandt et al. (2013) and Benson et al. (2015), other less commonly endorsed motives include recreational reasons (e.g., getting "high"), weight loss, and curiosity, and as many as 40% of students may engage in misuse for more than one reason (Benson et al., 2015).

Although most of the research concerning prescription stimulant misuse has been conducted with undergraduate student populations, research also has documented that misuse of prescription stimulants occurs among other demographic groups. A recent study of graduate students revealed a lifetime prevalence rate of approximately 17.5% (Verdi, Weyandt, & Zavras, 2014). In another study, adults between the ages of 18 to 49, recruited from the general population, reported past year prevalence rates of stimulant misuse of 2%, with 4.3% among those individuals ages 18 to 25, and 1.3% among participants ages 26 to 49 (Novak et al., 2007), and productivity and staying awake (i.e., cognitive enhancement) were two the most commonly reported motives for misuse behavior, similar to college students.

Although only a small number of studies have been conducted internationally, including in Germany, Iceland, and Switzerland, to name a few countries (e.g., Deline et al., 2014; Dietz et al., 2013; Gudmundsdottir & Weyandt, 2016; Mache et al., 2012; Maier, Liechti, Herzig, & Schaub, 2013), findings generally echo those from the United States. Specifically, academic and/or cognitive enhancement appears to be the primary motive for misuse behavior, and overall, male sex (Dietz et al., 2013; Gudmundsdottir & Weyandt, 2016), ADHD symptomatology (Gudmundsdottir & Weyandt, 2016), as well as psychological distress (e.g., Gudmundsdottir & Weyandt, 2016; Maier, Liechti, Herzig, & Schaub, 2013)

have been found to contribute significantly to misuse behavior. Prevalence rates of prescription stimulant misuse in these countries have ranged from approximately 3% to 13%, which indicates this behavior indeed occurs cross-culturally, highlighting the need for policy, prevention, and intervention to address this issue. To that end, identification of risk and protective factors is important; therefore, investigators have attempted to shed light on variables that may be predictive of prescription stimulant misuse behavior.

Factors Associated with Prescription Stimulant Misuse

Several demographic and psychological factors have been found to associate with prescription stimulant misuse. Although most of the risk factors have been identified within college student populations, several of them also apply to the general population. For example, based on data from the general population reported by Novak and colleagues (2007), misuse of stimulant medication appears to be more prevalent among young adults ages 18–25 than among individuals between the ages of 26–49. Additionally, a number of studies have reported higher rates of misuse among males than females (Darredeau, Barrett, Jardin, & Pihl, 2007; Dussault & Weyandt, 2013; Flory, Payne, & Benson, 2014; McCabe, Knight, Teter, & Wechsler, 2005; Novak et al., 2007; Rabiner et al., 2009), although a few studies have reported no significant differences based on gender (Benson et al., 2015; Sharp & Rosén, 2007). With regard to racial background, research has found higher rates of misuse among Caucasians than among individuals of other racial backgrounds (Dussault & Weyandt, 2013; Janusis & Weyandt, 2010; McCabe et al., 2011; Novak et al., 2007). Additionally, higher rates of misuse have been found among members of sororities or fraternities within American college student populations (McCabe et al., 2005; Rabiner et al., 2009; Weyandt et al., 2009) and students who have a lower grade point average (GPA) (DuPaul, Weyandt, O'Dell, & Varejao, 2009; Dussault & Weyandt, 2013; Rabiner et al., 2009). Procrastination and difficulty with time management have also been shown to relate to stimulant misuse among college students, specifically (Moore, Burgard, Larson, & Ferm, 2014). Additionally, researchers have reported higher rates of prescription stimulant misuse among individuals with a history of substance use (Novak et al., 2007) and other risky behaviors such as drinking and driving (McCabe et al., 2005).

Several psychological risk factors have been found to be predictive of prescription stimulant misuse, including symptoms of inattention (Arria et al., 2011; Rabiner et al., 2009), depression (Teter, Falone, Cranford, Boyd & McCabe, 2010), anxiety (Dussault & Weyandt, 2013; Verdi, Weyandt, & Zavras, 2014; Weyandt et al., 2009; Zullig & Divin, 2012), stress, internal impulsivity, and internal restlessness (Dussault & Weyandt, 2013; Verdi et al., 2014; Weyandt et al., 2009). Indeed, a recent meta-analysis found ADHD symptoms were significantly associated with prescription stimulant misuse (Benson et al., 2015). Further, Van Eck et al., (2012) found disinhibition and conduct problems symptoms moderated the association between ADHD symptoms and misuse of prescription stimulants among college students. Finally, Novak et al., (2007) reported higher odds ratios of stimulant misuse among individuals who had at some point been prescribed stimulant medication to treat ADHD.

Are Prescription Stimulants Truly Neurocognitive Enhancers?

A voluminous amount of data is available that supports the effectiveness of prescription stimulants in decreasing ADHD symptomatology; however, studies and reviews examining the cognitive effects of prescription stimulant medication in individuals with this disorder have found that these medications produce only modest effects at enhancing cognition in this population. For example, in a review of 36 placebo-controlled studies examining executive and non-executive neurocognitive outcomes, methylphenidate was shown to associate with small to moderate positive effects for memory, reaction time, reaction time variability, and response inhibition in children and adolescents (Coghill et al., 2013). Research including children and adults with ADHD has also demonstrated general improvements from amphetamine, methylphenidate, and modafinil in the areas of attention, impulsivity, memory and response inhibition (Weyandt et al., 2013). Regarding adult only samples with ADHD, a review conducted by Advokat (2010) found that amphetamine and methylphenidate have shown benefits for sustained attention (e.g., Barrilleaux and Advokat, 2009; Wilson, Cox, Merkel, Moore, & Coghill, 2006) and methylphenidate has demonstrated improvements for verbal memory performance over a period of up to 6 months (Kurscheidt et al., 2008) with inconsistent and non-significant findings occurring within some studies examining tests of distractibility (Advokat, 2010).

Given the high rates of prescription stimulant misuse among young adults *without* ADHD who report cognitive and/or academic enhancement as the primary reason for misusing stimulant medication (Advokat, Guidry & Martino, 2008; Bossaer et al., 2013; DeSantis, Webb & Noar, 2008; Garnier-Dykstra et al., 2012; Habibzadeh et al., 2011; Novak, Kroutil, Williams, & Van Brunt, 2007; Rabiner et al., 2009; Teter, McCabe, Cranford, Boyd, & Guthrie, 2005; White et al., 2006; Weyandt et al., 2009), the obvious empirical question is whether prescription stimulants truly enhance the cognitive and/or academic functioning of these individuals or whether they simply believe that they do. This is an especially intriguing question given that grade point average (GPA) has been found to be negatively correlated with stimulant misuse among college students (Benson et al., 2015; Weyandt et al., 2013).

A limited number of studies have attempted to address this question and results from three systematic meta-analyses (Ilieva, Hook, & Farah, 2015; Marraccini, Weyandt, Rossi, & Gudmundsdottir, in press; Repantis, Schlattmann, Laisney, & Heuser, 2010) and two reviews (Advokat, 2010; Smith & Farah, 2011) have also revealed small to moderate effects on behavior, with the greatest effects associated with long-term memory. As presented in Table 1, these studies investigated a variety of stimulant medication types and participants that differed on a number of dimensions, resulting in findings that both overlap and differ depending on the study design inclusion requirements. Of note, none of these studies restricted selection of studies based on type or dose of prescription stimulant beyond amphetamine and methylphenidate, allowing for all formulations of drugs. Only two studies (Ilieva et al., 2015; Marraccini et al., in press) explicitly accounted for dose as a moderating variable of interest. Most studies restricted participants to those who were “healthy” (i.e., without psychological or physical disorders) and who ranged in age from young to middle aged adults. Finally, the conceptualization of the underlying constructs of cognition varied across studies, resulting in a variety of instruments and measures of cognition. As presented

in Table 2, we considered findings separately for attention, executive function, cognitive control, memory and learning, and processing speed. Note, however, that there is considerable overlap among cognitive constructs and consequently, findings in each domain are likely influenced by one another.

Attention

Only one review (Repantis et al., 2010) examined the potential neurocognitive benefits of prescription stimulants (methylphenidate) on attention, which was measured by a variety of reaction time tests and included focused, selective, and divided attention. As can be seen in Table 2, when all types of attention were taken together, results were not statistically significant. It is important to note, however, that differential effects may exist based on type of attention. For example, previous research has found improvements in focused attention among adults without ADHD (Advokat, 2010).

Executive Function

Studies that examined the effects of prescription stimulants on executive functions included a variety of tasks that measured cognitive flexibility, calculation, verbal fluency, planning, and decision-making. In general, findings did not support prescription stimulant effects on domains of executive function (see Table 2). Among the studies examining verbal fluency and grammatical reasoning, one study supported methylphenidate benefits for complex verbal fluency; however, the majority of studies resulted in non-significant effects from both amphetamine and methylphenidate (Smith & Farah, 2011). Findings concerning planning and decision-making were similar, with no evidence to support methylphenidate enhancement or impairment of these domains of executive function (Marraccini et al., in press; Smith & Farah, 2011). It is important to note, however, that findings were limited by the inclusion of only a small number of studies and future research examining the influence of prescription stimulants on planning, decision-making, and cognitive flexibility is needed, prior to eliminating the possibility of cognitive impairment.

Cognitive Control

Findings from studies examining cognitive control, which involves the resisting of impulses and measures of cognitive flexibility or task-switching, were mixed, depending on the specific behavior measured (Smith & Farah, 2011). When taken together, significant but small effects of amphetamine and methylphenidate on inhibitory control were supported by a meta-analytic study (Ilieva et al., 2015), suggesting among healthy adults prescription stimulants proffer small benefits to cognitive control. When analyzed separately, however, benefits appeared to only occur within certain domains of cognitive control and for certain individuals. More specifically, Smith & Farah (2011) reported that both amphetamine and methylphenidate were associated with overall improvements (accuracy and/or speeded responses) in certain tasks of response inhibition (i.e., go/no-go, flanker, Stroop), as well as perceptual motor and delay rewards tasks. Results, however, were generally null or *impairing* for tasks of response inhibition requiring cancellation (i.e., stop signal tasks),

cognitive flexibility (i.e., Intra-Extra Dimensional Set-shift Task, Wisconsin Card Sorting Task), trail-making tasks and reversal learning tasks.

Advokat (2010) also reported increased errors and decreased response latencies on cognitive flexibility and set-shifting tasks (e.g., Intra-Extra Dimensional Set-shift Task, Wisconsin Card Sorting Task) associated with amphetamine and methylphenidate, suggesting that a worsening of distractibility may occur due to an increase in arousal resulting in more impulsivity in adults with higher baseline functioning. Preliminary findings from a meta-analysis examining the neurocognitive effects of prescription stimulants cognitive flexibility (Marraccini et al., in press), however, *did not* support Advokat's (2010) conclusions about impairments of cognitive flexibility. Although limited by a small number of studies ($k = 6$), results suggested that amphetamine and methylphenidate did not result in significant effects on cognitive perseveration. Finally, a consistent finding across studies that considered moderator variables of the effects of prescription stimulants on cognitive control indicated that the greatest benefits occurred for individuals with poorer task performance prior to treatment or those homozygous for the val allele (Smith & Farah, 2011).

Memory and Learning

Studies examining the cognitive effects of prescription stimulants on memory, which refers to the ability to retain and access information (Lezak et al., 2012), have focused on working memory (the ability to hold and work with information), declarative memory (explicit learning), and non-declarative memory (unconscious learning). Taken together, Repantis et al. (2010) examined four studies that supported positive and large effects of methylphenidate on both immediate and delayed working memory and episodic memory. Less clarity, however, emerged across studies examining working memory specifically. Smith and Farah (2011) reported findings from both amphetamine and methylphenidate that appeared mixed, with no indication that types of task influenced results; however, studies with significant findings also resulted in small to large effects. Indeed, significant but small effects of amphetamine and methylphenidate were supported for working memory in Ilieva et al.'s (2015) meta-analytic study.

Smith and Farah's review found evidence supporting benefits from amphetamine and methylphenidate on learning measured with both declarative and non-declarative tasks effects spanning a wide range of effect sizes. More specifically, effects were greatest when recall was delayed as opposed to immediate. A recent study supporting many of the conclusions drawn by Smith and Farah (2011) also reported significant but small effects of amphetamine and methylphenidate on short-term episodic memory, as well as moderate effects on delayed episodic memory (Ilieva et al., 2015). Delayed episodic memory results, however, were qualified by the potential for publication bias. Advokat's (2010) review also concluded that when prescription stimulants (both amphetamine and methylphenidate) are active during memory consolidation they may lead to improved long-term information retention, but otherwise they may have no effects, or negative effects, on short-term information acquisition.

Finally, tasks that involved non-explicit or nondeclarative learning and memory, which involve an unconscious remembering of knowledge (Lezak et al., 2012), were generally null for amphetamine and methylphenidate effects on immediate tasks across studies (Smith & Farah, 2011); however, one study reported improved speed (i.e., response processing) from amphetamine, and one study reported enhanced learning over time from amphetamine. Regarding associative learning tasks, findings from Advokat (2010) and Smith & Farah (2011) generally did not support benefits from methylphenidate and amphetamine, with only one study demonstrating immediate improvements from amphetamine in semantic learning.

Similar to previously described domains of cognition, conclusions drawn across studies examining the influence of prescription stimulants on memory also suggested that both baseline functioning and genotype variability may influence the effects of prescription stimulants, i.e., those with lower baseline functioning may receive the greatest benefits towards memory acquisition (Advokat, 2010; Smith & Farah, 2011). Findings, therefore, collectively indicate that it is essential to consider individual characteristics when determining whether or not prescription stimulants enhance cognitive functioning.

Processing Speed

Although only one of the included studies (Marraccini et al., in press) examined the effects of prescription stimulants on processing speed, it is important to note that many of the previously described constructs may have considerable overlap with processing speed (e.g., trail making tasks, response time tasks, etc.). Nonetheless, findings from this study are notable in that significant and small effects of amphetamine were found to benefit processing speed (Marraccini et al., in press).

Potential Moderating Variables

Findings from a single study examining both the objective and subjective cognitive effects of amphetamines among healthy adults (Ilieva, Boland, & Farah, 2013) point to the potential for the placebo effect to account for perceived cognitive enhancement. Specifically, findings *did not* support significant effects of amphetamine on episodic memory, working memory, inhibitory control, creativity, intelligence and scholastic achievement among the general sample, but they did support perceived enhancement. In other words, participants may not have derived any neurocognitive benefits from amphetamine, but they perceived positive neurocognitive effects. These findings point to a potential reason for the popularity of misusing prescription stimulants for neuroenhancement and the need for further randomized clinical trials accounting for the placebo effect.

Findings from the majority of the studies also highlighted important moderators that may explain variability across level of enhancement. As noted before, general effects of amphetamine on cognition were not observed; however, both baseline ability and catechol-*O*-methtransferase (COMT) genotype emerged as potential moderators on word recall and measures of creativity where positive effects were robust for participants with lower baseline functioning, i.e., lower cognitive functioning, and those who were homozygous for the *val* allele of the COMT gene. Although previous reviews (Smith & Farah, 2011) have drawn

similar conclusions about the importance of baseline functioning and COMT genotype, only a few other studies have explored these variables as moderators of prescription stimulant medication on cognition (e.g., Mattay et al., 2003; Wardle et al., 2013) and conclusions have been mixed.

A critical moderator of interest across these studies includes the potential for differences of effects according to medication dose. All of the review and meta-analytic studies included studies that examined cognitive effects of methylphenidate and/or amphetamine across any dose level; however, the majority of studies included in these studies used doses that ranged between 10–20 mg for both drug types. Both Ilieva et al. (2015) and Marraccini et al. (in press) included dose level (low versus high) as a moderator variable of interest. Among the constructs examined in these studies, only delayed episodic memory demonstrated significantly different results based on dose. Specifically, studies with low doses, which also exclusively included studies with male participants only and retention of memory assessed at greater intervals, demonstrated the greatest effects (Ilieva et al., 2015). Although dose level was not analyzed as a separate moderating variable in any of the additional reviews, the wide range of doses and inconsistent results suggest the need for a more systematic investigation of the differential cognitive effects according to dose. Indeed, Repantis et al. (2010) explained that considering methylphenidate may follow an inverted U-shape function, additional research investigating how dose levels may impact cognitive enhancement is warranted. Smith & Farah (2011) point out a similar issue across methylphenidate and amphetamine, highlighting the importance of considering the nonmonotonic effects of these drugs, wherein higher than optimal doses may lead to impairments. Although the researchers explain that the studies included in their review did not demonstrate pronounced effects across dose level, Smith and Farah noted that optimal doses are influenced by additional characteristics often not accounted for in study designs. Thus, a lack of understanding in variability according to dose level and individual variability is a clear limitation across the majority of studies examining the potential for neurocognitive enhancement from prescription stimulants.

Findings from this review also highlight the need for a more thorough understanding of the effects of repeated administration of prescription stimulants, as opposed to single dose administrations of stimulants. Although two of the reviews (Repantis et al., 2010; Smith & Farah, 2011) included studies that assessed either single or repeated administration of drugs, the vast majority of included studies assessed single drug administration only, precluding a thorough examination of the influence of repeated drug administration. Future research that explicitly examines repeated drug administrations, accounting for timing of dose, is warranted.

Cognitive Enhancement Summary

In summary, preliminary empirical evidence supports that individuals with and without ADHD may receive small to moderate cognitive benefits from taking prescription stimulant medications in the areas of working memory, response inhibition, processing speed, and delayed memory. In contrast, preliminary findings, although limited by a small number of studies, generally do *not* support significant effects of prescription stimulants on various

behavioral measures of attention, executive function (e.g., decision making, verbal fluency, and planning), reversal learning, or cognitive flexibility. The mechanisms explaining neurocognitive enhancement, however, are less understood. For example, it is possible that neuroenhancement is better explained by placebo effects, altered perception of quality of work, or enhanced energy and motivation to improve productivity (Hildt, Lieb, & Franke, 2014; Ilieva et al., 2015; Smith & Farah, 2011). Mixed findings across studies examining the cognitive effects of prescription stimulants may also be explained by limitations inherent to comparing findings across a variety of study designs, as well as limitations concerning study design itself (i.e., power limitations, generalizability issues, poor psychometric properties of outcome instruments, and variability across doses). Furthermore, there are a number of important moderator variables that may explain inconsistent findings; for example, individuals with poorer baseline functioning as well as those who are homozygous for the val allele may derive benefits from prescription stimulants. Findings from studies accounting for dose level (Ilieva et al., 2015; Marraccini et al., under review) did not indicate differences across low and high doses; however, more explicit examination of the influence of doses is warranted.

Unanswered Questions and Future Directions

As noted previously, preliminary studies suggest prescription stimulants may proffer modest effects for cognitive neuroenhancement in adults in general; however, additional, double-blind, placebo-controlled studies are needed to adequately address this issue with healthy controls. Unequivocally, college students, specifically, are misusing prescription stimulants for academic enhancement at high rates; yet, empirical studies are lacking that address whether student memory, reading comprehension, writing performance, exam performance, presentation skills, and other college-based skills are truly enhanced. In addition, future studies are needed to elucidate whether and how baseline cognitive functioning, genetic factors, timing of medication ingestion relative to assessment of performance, medication doses, medication formulations, and different tasks moderate the effects of stimulants on performance. Double-blind placebo controlled studies designed to examine individual components of cognition as well as ecological measures, such as exam performance, assignments, and presentations, are sorely needed to adequately address the question of whether prescription stimulants enhance cognitive functioning in healthy adults.

Misuse of prescription stimulants is considered a felony in many states and individuals who are caught engaging in this behavior may face judicial consequences. So what is driving this behavior? There are a number of plausible reasons young adults may be drawn to a quick fix, to become “limitless” and to be able to “power through” work. With regard to undergraduate students, many perceive the college environment as fast-paced and high-pressured; yet, distractions abound on a daily basis (e.g., extracurricular activities, social events, social media, etc.). Hence, it is no surprise that some students fall behind, their academic performance is hindered, and they seek assistance via stimulants to improve their performance (DuPaul et al., 2009; Dussault & Weyandt, 2013; Rabiner et al., 2009). Indeed, research supports that students who are more disorganized (Moore et al., 2014), have poorly developed study skills (Arria, O’Grady, Caldeira, Vincent, & Wish, 2008) and those who have a sense of internal restlessness (Dussault & Weyandt, 2013; Verdi et al., 2014; Weyandt

et al., 2009) and are attracted to risk-taking behavior (McCabe et al., 2005), are more likely to misuse prescription stimulants.

In addition to the health and legal risks associated with prescription stimulant misuse, it is often regarded as “cheating” by university honor codes (Schwarz, 2013), as well as within research (Goodman, 2010), and has been compared to the illicit use of steroids for athletic performance enhancement (Dodge, Williams, Marzell, & Turrisi, 2012; Marraccini et al., under review). Student beliefs around this issue, however, are mixed. For example, 33% of Ivy League students did not perceive stimulant misuse as a form of cheating, while 41% thought it was cheating, and another 25% were unsure (Colaneri, John, & Adesman, 2014). Moreover, Dubljević, Sattler, and Racine (2014) revealed a small correlation between student use of cognitive neuroenhancers and reported plagiarism and fabrication. In yet another study, Dodge and colleagues (2012) reported that college freshman rated an athlete misusing anabolic steroids at a sporting event as “more of a cheater” than a student misusing Adderall during midterm exams. Interestingly, this difference became larger as past prescription stimulant misuse increased. Results from this study also demonstrated that participants believed Adderall was more necessary than anabolic steroids for bringing about success (Dodge et al., 2012). Collectively, current studies suggest that a majority of college students do not perceive prescription stimulant misuse as unethical compared to acts typically considered as cheating (e.g., plagiarism, looking at a peer’s test, notecards/cheat sheets). Although use of stimulants without a valid prescription is an illegal activity, the extent to which faculty and the administration view misuse of stimulants as cheating remains unexplored. Given the discrepancy between the illegal misuse of prescription stimulants and student views of prescription stimulant misuse as largely academically acceptable, it may be prudent for universities to provide explicit examples of cheating, including the misuse of prescription stimulants, within their academic honesty policies.

Alternatively, society may choose to embrace “cosmetic” psychopharmacology due to the small, but significant cognitive effects found across multiple cognitive domains (Greely et al., 2008; Kramer, P., 1993; Marraccini et al., under review; Sahakian & Morein-Zamir, 2007). Proponents of this approach maintain that allowing anyone (medically supervised) access to these medications, regardless of ADHD status, may ultimately allow humans to reach their maximum cognitive potential (Dubljević, 2013; Greely, 2013). Greely (2013) suggests that although prescription stimulants may appear to be distinctive among cognitive enhancers provided their brain-altering effects, they are not, given that many interventions deliver neuroplastic, brain changes. For example, research has identified beneficial neural changes produced by instruction (Draganski at al., 2004), reading (Schlaggar & McCandliss, 2007), exercise (Hillman, Erickson, & Kramer, 2008), sleep (Vastag, 2004; Boonstra, Stins, Daffertshofer, & Beek, 2007), and nutritional factors (Almeida et al., 2002). Use of prescription stimulants, prophylactically has also been shown to decrease the likelihood of the emergence of certain disorders and behaviors, such as, major depressive disorder, anxiety, oppositional defiant disorder, and antisocial behavior, and reducing aggression (Biederman, Monuteaux, Spencer, Wilens, & Faraone, 2009; Connor, Glatt, Lopez, Jackson, & Melloni, 2002). It can be argued, therefore, that using prescription stimulants for neurocognitive enhancement may be considered similar to the more familiar methods of prophylactic intervention (Greely, 2013). Despite the various beliefs surrounding use of

prescription stimulants as neurocognitive enhancers, these medications are currently being misused at notably high rates and the rates appear to be increasing, at least among college students (Weyandt et al., 2013). It is imperative that greater discussion, research, and public policies be developed to address this societal issue.

In addition to ethical considerations pertaining to cheating, academic dishonesty, or "cosmetic" neuroenhancement, are the potential for medical complications when prescription stimulants are taken without medical supervision. The ultimate question to be addressed, therefore, is whether the benefits outweigh the risks for students desiring to misuse prescription stimulant medications. Presently, many individuals appear to view the benefits as outweighing the risks and in fact, college students frequently do not perceive misuse of these medications as posing risk. For example, Weyandt et al. (2009) revealed that college students often perceive misuse of stimulants as "safe" and DeSantis and colleagues (2008) found that 81% of college students interviewed considered illicit use of ADHD medication as either "not dangerous at all" or only "slightly dangerous". Research has demonstrated, however, that common side effects of prescription stimulants include sleep difficulties, increased wakefulness, suppressed appetite, agitation, increased physical activity, and cardiac symptoms, (Craig, Davies, Schibuk, Weiss, & Hechtman, 2015; Weyandt et al., 2014), and they have a high potential for misuse that may lead to psychological and/or physiological dependence (Kollins, 2003). In 2007, amphetamines and methylphenidate were ranked as 6th and 12th, respectively, for substances known to cause physical harm and 8th and 13th to cause dependence (Nutt, King, Saulsbury, & Blackemore, 2007). Although some of these side effects may be seen as beneficial in the short-term (e.g., wakefulness, increased physical activity), it is unclear whether regular, long-term misuse results in persistent disruptions within these or other domains of functioning.

Additionally, without medical observation, side effects could potentially lead to other serious conditions, leading the FDA to place a black box warning on prescription stimulant medication in 2006. Students who are given or who purchase prescription stimulants from others are taking a risk regarding the authenticity of the stimulant, the dose, side effects, and not knowing whether they have underlying cardiovascular problems that may be exacerbated by psychostimulant use (Nissen, 2006).

Considering that prescription drugs are second, only to marijuana, over any illicit substance for misuse liability among young adults (Substance Abuse and Mental Health Services Administration, 2012), there is a critical need for policy-makers, physicians, educators, and families to address the issue of prescription stimulant misuse. A related concern is that more than 50% of nonmedical prescription stimulant users have been found to report using other prescription drugs (e.g., opioids, sedatives, tranquilizers) in conjunction with stimulants (Chen et al., 2014). A recent report indicates that users who obtained stimulants from illegal sources had the highest prevalence of misuse of other prescription drugs (66.3%), closely followed by those who obtain their stimulants via physician sources (58.8%) (Chen et al., 2014). Unfortunately, it does not appear to be common practice for universities and primary care physicians to discuss misuse, diversion, potential consequences and side effects of other drug use along with prescription stimulant use (McCabe, Boyd, Couper, Crawford, & d'Arcy, 2002; Tarn et al., 2006). In fact, McCabe and colleagues (2002) reported that nearly

half of physicians sampled in their study found it difficult to discuss abuse potential of prescription drugs with their clients. Pediatricians and physicians may benefit from greater training regarding ways in which to distribute information concerning the potential dangers, judicial consequences of, and risks associated with drug misuse.

Prevention and intervention efforts targeting individuals identified to be most at risk for initiating prescription stimulant misuse could help mitigate this growing problem. For example, data from the *National Surveys on Drug Use and Health 2004–2012* indicated that the majority of first time prescription stimulant misuse occurs during adolescence and young adulthood between the ages 16–19. We strongly recommend that interventions that are designed to challenge expectancies around prescription stimulant use should target middle school, high school, and college students. For example, preliminary research indicates that an expectancy challenge intervention focused on modifying non-prescription stimulant use expectancies and reducing stimulant misuse holds the potential for reducing stimulant misuse among college students (Looby, De Young, & Earleywine, 2013). Further investigations, however, should examine the potential for more intensive interventions to maintain effects over time considering effects diminished by 6 weeks post intervention (Looby et al., 2013).

Although general knowledge of the ethical and medical concerns associated with prescription stimulant misuse may be minimal, many individuals may have even less understanding of the illicit nature of stimulant misuse. As noted previously, prescription stimulants are classified as Schedule II substances by the DEA (Drug Enforcement Administration, U.S. Department of Justice, 2015). Despite their illegality, stimulant medications are typically regarded as easily accessible by college students (McCabe et al., 2005; Rabiner et al., 2009; Sharp & Rosen, 2007; Weyandt et al., 2009), and are usually procured from peers or family members holding a valid prescription (Benson et al., 2015; Weyandt et al., 2013). Although drug regulations may vary between states, a non drug-addicted person guilty of possessing a schedule II controlled substance (e.g., prescription stimulants), may face consequences including, “imprisonment to a term up to life or fined not more than five hundred thousand dollars ($500,000) nor less than ten thousand dollars ($10,000), or both” (Uniform Controlled Substance Act, 2016).

In conclusion, despite the ethical, medical, and legal ramifications of prescription stimulant misuse, these medications continue to be misused primarily for cognitive enhancement, and secondarily for recreational purposes (Weyandt et al., 2013). Preliminary studies suggest that prescription stimulants may improve some aspects of cognitive functioning (e.g., as previously discussed, inhibitory control, working memory, short-term and delayed episodic memory, and processing speed) in healthy adults without ADHD but many of these studies are characterized by methodological limitations including low statistical power. To adequately address the empirical question of whether prescription stimulants such as Adderall truly enhance cognitive functioning, double-blind, placebo-controlled studies with healthy adults are needed. In addition, it is critical that potential moderators (e.g., baseline cognitive functioning) of the effects of stimulants on performance be considered in future studies.

In the meantime, until research clearly determines whether prescription stimulants enhance cognitive functioning and academic performance, and until empirically-based interventions are developed to decrease prescription stimulant misuse, students should be encouraged to err on the side of caution and be informed that the potential risks outweigh the current known benefits. We specifically encourage educators, given the prevalence of this behavior among student populations, to consider research findings concerning at-risk groups (i.e., Caucasian males, adolescents aged 16–19, students with a lower GPA, those engaged in Greek life on college campuses, students looking to lose weight or have an eating disorder) and to develop evidence-based outreach efforts to help decrease stimulant misuse within these groups. Continued efforts should be invested in offering assistance to students to help develop effective study habits, effective coping skills for managing stress, and encouraging use of available and readily accessible mental health resources to address psychological issues (anxiety, internal restlessness, depression) that appear to place students at greater risk for misusing prescription stimulants. Lastly, given recent findings that suggest the peak age of onset for first time misuse of prescription stimulants is during high school, it is critical that empirically based prevention programs be developed to help decrease the likelihood of prescription stimulant misuse among our nation's youth.

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Public Health Significance Statement

These findings suggest that misuse of prescription stimulants has become increasingly problematic among our nation's youth, with particular concern regarding age of first misuse and prevalence. As it stands, the potential risks involved in stimulant misuse outweigh any currently known benefits.

Table 1

Reviews and meta-analyses investigating cognitive enhancement of MPH and AMP

		Inclusion Criteria					
Study	**Type**	**Study Design**	**Participant Characteristics**	**Participant Age Range**	**Stimulant Type(s) (formulation)**	**Stimulant Dose Criteria (included dose range)**	**Variables Accounted For/ Moderator Variables**
Advokat (2010)	Review	Not reported	"Normal adults" (no psychological or neurological disorders), primarily male, college students	NR	AMP (amphetamine sulfate, d-amphetamine), MPH (NR)	Any dose (AMP: 10–15mg or 0.20–0.5mg/kg; MPH: 0.1kg/mg–40mg)	Drug type
Ilieva et al. (2015)	Systematic meta-analysis	Double blind, placebo controlled	Young and middle-aged healthy adults (no child or adult participants who were mentally ill, criminals, or elderly)	18–50	AMP (NR), MPH (NR)	Any dose (AMP: 5–20mg; MPH: 10–40mg)	Drug type Dose level (high, low) Caffeine restriction Gender distribution Risk of ceiling/ floor effects Reason to publish if effects are null Stimulus type (for WM only)
Marraccini et al. (in press)	Systematic meta-analysis	Double blind, placebo controlled	Healthy adults (no special groups or sleep deprived individuals)	Mean: 18–62	AMP (NR), MPH (NR), included only short-acting agents	Any dose (AMP: 0.14–0.43mg/kg; MPH: 15–40mg),	Stimulant type Dose level (high, low) Sex distribution Age Inclusion of non-behavioral tasks Timing of dose activation

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		Inclusion Criteria					
Study	**Type**	**Study Design**	**Participant Characteristics**	**Participant Age Range**	**Stimulant Type(s) (formulation)**	**Stimulant Dose Criteria (included dose range)**	**Variables Accounted For/ Moderator Variables**
Repantis et al. (2010)	Systematic review and meta-analysis	Single- or double randomized or quasi-randomized controlled clinical trials (cross-over and parallel)	Healthy individuals (no evidence of psychiatric disorder, cognitive decline, or other diseases) any age	Mean: 20–70	MPH (NR), extended release and short-acting agents, Modafinil (findings not presented here)	Any dose level (5–45mg)	Due to limited variability, single drug vs.repeated drug and dose level were not included as covariates
Smith & Farah (2011)	Review	Placebo-controlled design	Non-elderly adults (no patient groups)	18–45	AMP (d-AMP by itself or as the primary ingredient in Adderall), MPH (e.g., Ritalin)	Any dose level (AMP: 0.035–0.5mg/kg; MPH: 5-mg–60mg)	Task Timing

Note. AMP = amphetamine; MPH = methylphenidate; NR = not reported; WM = working memory

Table 2

Findings per outcome based on reviews and meta-analyses investigating cognitive enhancement of MPH and AMP

Outcome Construct by Study	Measures	*k*	Overall Findings	Summary & Recommendations
Attention				
Repantis et al. (2010)	Reaction Time tests Stroop Colour Word Test Compensatory Tracking Task, Divided Attention Task Mackworth Clock Test	10	NS association between MPH and attention (d = 0.397 (CI −0.320, 1.113), *NS*).	Findings did not support PS effects on a variety of measures of attention (e.g., selective, divided, sustained). Future research should examine differences across individual domains of attention.
Executive Function				
Repantis et al. (2010)	Tasks of cognitive flexibility Information processing tasks Calculation tasks Logical reasoning tasks Gambling tasks Probabilistic learning tasks Verbal fluency tasks	3	Association of MPH and various tasks of EF were NS: (Time 1: d = 0.92 (CI −0.236, 2.072), *NS*; Time 2: d = 1.085 (CI −0.154, 2.323), *NS*).	Preliminary research suggests that various aspects of executive functions, including decision-making, verbal fluency, and planning, are not significantly impacted by AMP or MPH.
Smith & Farah (2011)	Verbal fluency tasks Sequence generation Raven's Progressive Matrices TOL, NTOL Grammatical reasoning tasks Strategic choice task	5	The majority of studies examining the influence of AMP and MPH on executive function were NS.	Given the low number of studies within this domain of cognition, additional research is needed to clarify how/whether PS contribute to EF performance.
Marraccini et al. (under review)	Iowa Gambling Task – advantageous decision making TOL, NTOL – planning accuracy, planning time	5	PS and advantageous decision-making were not significantly associated: g = −0.191 (95% CI −0.561, 0.180, p = .313). PS and planning accuracy were not significantly related: g =0.048 (95% CI −0.194, 0.290), p = .698) or planning time, g = −0.140 (95% CI −0.383, 0.102, p = .257).	
Cognitive Control				
Ilieva et al. (2015)	Stop signal task Go/no-go Wisconsin Card sort ID/ED Flanker Stroop Antisaccade task	24	Findings supported small, significant effects of MPH and AMP on inhibitory control compared to normative functioning (g = 0.20 (CI, 0.11, 0.30) and gain scores (g = 0.19 (CI 0.11, 0.26). No moderator variables (including dose) were significant.	Findings suggest MPH and AMP result in modest benefits for inhibitory control; however, result varied based on task and may have differential effects across individuals, i.e.,,preliminary research indicates individuals with lower baseline functioning (or homozygous for the val allele) may receive the greatest benefits. Future research should continue to examine how baseline functioning potentially moderates the relationship between PS and measures of cognitive

Outcome Construct by Study	Measures	*k*	Overall Findings	Summary & Recommendations
Smith & Farah (2011)	Go/no-go Stop-signal task Stroop test WCST Attentional set-shifting (IDED) Reversal learning TMT Flanker test Stimulus evaluation/response selection task Delay discounting Delay gratification	16	Taken together, studies examining cognitive control resulted in mostly mixed findings; however, the greatest benefits appeared to be for those with poorer baseline functioning or those homozygous for the val allele	control, and whether they may potentially impair performance.
Advokat (2010)	Attentional Set-Shifting Tasks Tests of perseveration (i.e., WCST)	2	Findings demonstrated preliminary support for impairments in cognitive flexibility.	
Marraccini et al. (under review)	WCST, IDED – perseveration	6	PS was not significantly associated with cognitive perseveration, g =0.003 (95% CI −0.095, 0.101), p = .949). Moderator analyses were not significant.	
Memory and Learning				
Repantis et al. (2010)	List learning tests (with acquisition trials and recall and recognition) Visual Memory Spatial Memory Working Memory	4	MPH was associated with positive benefits for memory and learning across immediate and delayed time points: Time 1: d = 1.4, (CI 0.42, 2.38), p < .007; Time 2: d = 1.37, (CI 1.46, 2.59), p < .03).	Findings indicate MPH and AMP may improve some aspects of memory and learning and are especially robust for delayed memory. Future studies should continue to investigate potential moderators, including baseline levels of functioning, genetic factors, and timing of PS intake,
Working Memory				
Ilieva et al., 2015	*n*-back Rapid information processing Sternberg Digit span CANTAB spatial working memory Spatial delayed response	23	Findings supported small, significant effects of MPH and AMP on WM when compared to normative functioning g = 0.13, CI (−0.02, 0.27), and gain scores, g = .130, CI (0.06, 0.20). Moderator analyses were not significant across variables of interest.	
Smith & Farah (2011)	Item recognition *n*-back CPT Digit span Spatial span Pattern memory	23	Findings across studies were mixed with no indication that types of task influenced results.	
Declarative and Non-declarativec Memory				
Advokat (2010)	Acquisition and recall of word lists and stories, typically 30–180 min after ingestion Light learning test	11	Results suggested AMP and MPH do not improve memory consolidation or short-term memory acquisition, but may benefit consolidation and recall when ingested after learning.	
Ilieva et al. (2015)	Recall (free and cued) and recognition tests	12, 11	Results supported small, significant effects for immediate memory (k = 12) compared to normative functioning, g = 0.20, 95% CI	

Outcome Construct by Study	Measures	*k*	Overall Findings	Summary & Recommendations
			0.01, 0.38) and gain scores, *g* = 0.22, 95% CI (0.09, 0.35]. No moderator analyses were significant. Effects for delayed memory were moderate and significant (k = 11) compared to normative functioning, *g* = .45, 95% CI [0.27, 0.63] and gain scores, *g* = .44, 95% CI [0.26, 0.62]. Larger effects were found among males in studies with low doses of medication, and results were qualified with potential for publication bias.	
Smith & Farah (2011)	Verbal learning Associative learning Probabilistic learning Motor sequence learning	22	Evidence supported small to large positive effects from PS on learning measured with both declarative and non-declarative tasks	
Processing Speed				
Marraccini et al. (under review)	DSST	8	Findings supported small, significant effects for processing speed, *g* = 0.282 (95% CI 0.077, 0.488, *p* = .007), with indication for publication bias. No moderator analyses were significant.	Preliminary findings indicate PS associate with increased processing speed accuracy; however, more studies examining this domain of cognition are needed.

Note. AMP = amphetamine; CANTAB = Cambridge Neuropsychological Test Automated Battery; CI = Confidence Interval; CPT = Continuous Performance Task; DSST = Digit Symbol Substitution Task; EF = Executive Function; IDED = Intra-Dimensional/Extra-Dimensional (set shifting); MPH = methylphenidate; NS = nonsignificant; NTOL = New Tower of London; PS = Prescription Stimulants; TMT = Trail Making Test; TOL = Tower of London; WCST = Wisconsin Card Sorting Test; WM = Working Memory.