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Contrast of Medical and Nonmedical Use of Stimulant Drugs, Basis for the Distinction, and Risk of Addiction: Comment on Smith and Farah (2011)

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Abstract

Smith and Farah (2011) presented a scholarly review of critical areas related to their intriguing title “Are Prescription Stimulants ‘Smart Pills’?” We contend that they accomplished the main goal of the article, to get the facts straight about possible cognitive enhancement via the nonmedical use of stimulant drugs by individuals without a diagnosis of attention-deficit/hyperactivity disorder (ADHD). At the same time, they justified their main conclusions that (a) individuals are seeking and engaging in nonmedical use of stimulant drugs with the expectations of cognitive enhancement despite uncertainty whether such expectations are valid and (b) on some tasks, there are small average benefits of nonmedical use, but the overall pattern is not clear (e.g., small beneficial effects across most individuals or large beneficial effects only in a few individuals, both of which result in small average effects). We offer comments in 3 areas to amplify key topics mentioned but not emphasized by Smith and Farah: (a) characterization of the cognitive effects of medical use of stimulants to contrast with the cognitive effects of nonmedical use; (b) justification of medical use of stimulants by placement on a normally distributed dimension of behavior rather than categorical diagnosis of ADHD, which varies widely across countries; and (c) evaluation of the potential risks of nonmedical use to individuals and to society (e.g., the likelihood of addiction to stimulant drugs in a small minority of the population) rather than just the potential benefits of cognitive enhancement.

Keywords

ADHD; stimulant drugs; medical use of stimulants; diversion of stimulants; addiction to stimulants

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A primary purpose of the article “Are Prescription Stimulants ‘Smart Pills’?” (Smith & Farah, 2011) was to address the possibility of cognitive enhancement associated with the nonmedical use of stimulants by individuals without a diagnosis of attention-deficit/hyperactivity disorder (ADHD). To accomplish this aim, Smith and Farah (2011) used six questions to organize the literature: How widespread is the nonmedical use of prescription stimulants? Who uses them and why? How are these controlled Schedule II drugs obtained? Does the nonmedical use of stimulants enhance cognition as intended? What aspects of cognition might be enhanced? What subgroups might benefit most?

To complement and extend this substantial contribution, we offer commentary in three areas that were not covered in detail but are relevant to this controversial and important topic. We have addressed these areas in recent articles that we summarize and expand here. First, we use the organization provided by Smith and Farah (2011) to address how their six key questions are related to the medical use of stimulants and cognitive effects in individuals with ADHD (see Swanson, Baler, & Volkow, 2011), and we amplify their review of nonmedical use with consideration of the total use of stimulant drugs in the U.S.A. relative to other countries (see Swanson & Volkow, 2009). Second, we discuss the rationale for justifying medical use of stimulants based on placement on a dimension of behavior rather than by categorical diagnosis of ADHD, which provides a different perspective on ethical and legal issues (see Swanson, Wigal, Lakes, & Volkow, 2011). Third, we discuss our previously expressed concerns about addictive properties of stimulant drugs (see Swanson & Volkow, 2008; Volkow & Swanson, 2008), based on the assumption that abuse and dependence are inevitable in a small but significant minority of individuals engaged in nonmedical use of stimulants.

Six Questions About Medical Use of Stimulants

How Widespread Is the Total Use of Stimulants?

An estimate is provided by annual reports of the International Narcotics Control Board (INCB) of the United Nations, which put medical and nonmedical use into historical and worldwide perspectives (Swanson & Volkow, 2009). Commissioned in 1971 by the Convention on Psychotropic Substances, the INCB tracks the disposition of the worldwide production of all Schedule I, II, III, and IV drugs. Methylphenidate (MPH) and amphetamine (AMP) are classified as Schedule II drugs (those with recognized medical uses that, when abused, may lead to severe psychological or physical dependence). In the 1960s and 1970s, there was widespread overprescription of MPH and AMP (e.g., mostly written for non-ADHD adults as “diet pills” or “pep pills”), rampant diversion of these stimulants, and an epidemic of abuse and dependence (see Berman, Kuczenski, McCracken, & London, 2009; Grinspoon & Hedblom, 1975; Rasmussen, 2008), which contributed to the creation of the INCB.

The reports of the INCB provide annual estimates of national drug supplies conditional on each nation's population, defined as the statistical defined daily dose (S-DDD) per 1,000 individuals. For stimulants, the values adopted in 1971 for reporting purposes were 30 mg/day for MPH and 15 mg/day for AMP. These values proved to be accurate for the therapeutic daily dose determined by modern titration algorithms applied to treat children diagnosed according to current criteria for ADHD (e.g., for MPH, Greenhill et al., 2001, reported an average titrated dose of 28–32 mg/day).

After the imposition of monitoring and controls in 1971, the worldwide production and supplies of MPH and AMP fell dramatically, and the national supplies for the U.S.A. followed this trend. However, in the 1990s, the U.S.A. supplies increased rapidly. By monitoring the INCB annual reports, we noticed this fact promptly (Swanson, Lerner, &

Williams, 1995) and called attention to a large (almost 300%) increase in the U.S.A. supply of MPH from 1990 to 1994. We assumed that this sudden increase was due to the convergence of two historic events: (a) the formation of large national parent advocacy groups (e.g., Children and Adults With ADD) in the late 1980s that reduced stigma and increased recognition of ADHD and (b) changes in federal educational law (i.e., the 1990 Individuals With Disabilities Education Act) that recognized ADHD as an educational disability and made provisions for school-based services. We reasoned that the annual increases would eventually decrease because an asymptote would occur when the supply met the increased demand for medical use of stimulants elicited by the unusual events.

However, an asymptote has not yet occurred. Instead, after 1995, a linear increase in S-DDD based on the supply for the U.S.A. was maintained for more than a decade (Swanson & Volkow, 2009). The most recent INCB report showed that by 2008, the S-DDD for MPH was 12.03 per 1,000 and, for AMP, it was 8.97 per 1,000, for a combined total S-DDD of 21.0 per 1,000 individuals (INCB, 2009). On the basis of the U.S. Census estimate of the 2008 population of the U.S.A. (304,374,846), the INCB supply would be sufficient to treat 6,391,872 individuals for all 365 days of the year (U.S. Census Bureau, 2009, Table 1). Compared to rates of use in the other 20 countries listed in the INCB report, the combined MPH-AMP rate for the U.S.A. (21.0) is almost double that of the next highest country (11.15 for Iceland) and about 6 to 10 times that of the middle five countries (from 3.67 for the United Kingdom to 2.13 for Belgium). Despite the historic high level of supply, shortages for medical use in the U.S.A. have recently occurred (see U.S. Food and Drug Administration, 2011). Since the supply is set each year based on the projections of medical need, this provides the basis for continuing increases in supply in the future. However, the shortage may be the result of increases in nonmedical as well as medical use of stimulants, which may complicate the rationale for increases in supply prompted by shortages.

As we have discussed in detail elsewhere (Swanson & Volkow, 2009), if the true prevalence of ADHD is the same across countries, as is generally assumed, then such drastic national differences in supplies of stimulants and national treatment rates would complicate cross-national comparisons and would create cross-national differences in the concepts and meanings of medical and nonmedical use. For example, if the high rate of medical use in the U.S.A. were considered inappropriate by practitioners and policy-makers in other countries, they might consider a large component of the S-DDD of the U.S.A. to be mislabeled nonmedical use. On the other hand, if individuals are engaged in nonmedical use to achieve self-medication of ADHD, then a component of nonmedical use in those countries might be considered appropriate medical use by practitioners and policy makers in the U.S.A.

How Much of the Total Supply of Stimulants Goes to the Intended Medical Use?

Firm estimates are not available, but we have developed a strategy to investigate this issue by comparing estimates of national supply to estimates of national prevalence of use. The National Survey of Children's Health (NSCH), conducted by the U.S. Centers for Disease Control (CDC), in 2007–2008 estimated that 4.8% of children between 4 and 17 years of age (about 2.7 million children in the U.S.A.) had a current diagnosis of ADHD and were being treated with stimulant medication (see Visser, Bitsko, Danielson, & Perou, 2010). The 2008 S-DDD of 21.0 established that the supply could treat 6,391,872 individuals across all ages, as discussed above. To estimate how many of these individuals were in the CDC-NSCH age range, we used prescription records from a national database (SDI Vector One: National, http://sdihealth.com/vector_one/national.aspx), which reported that 60% of the annual prescriptions for MPH and AMP in 2008 were written for children between 4 and 17 years of age. Applying this to the number of individuals in this age segment of the population of the U.S.A., this suggests that about 3.84 million individuals would be engaged in medical use if all of the prescriptions were used as intended.

We reasoned that the ratio of actual use to potential use—2.7 million/3.84 million = 0.70—might represent how much of the supply was used as intended. Recent estimates of prevalence of ADHD diagnoses in other age segments of the population are not available for 2008 (e.g., for adults, the most recent estimates were from National Comorbidity Survey Replication conducted in 2002; see Kessler et al., 2006), so we do not have equivalent estimates for 2008 of the ratio of observed use and potential use for children below 4 years of age or adults above 17 years of age.

How Many Prescriptions for Medical Use of Stimulants Are Being Diverted to Nonmedical Use?

If our rough estimate for school-age children is correct (and holds for other segments of the population) and only 70% of the 2008 supply of stimulants was devoted to medical use, then we speculate that the remainder (30%) may have been diverted to nonmedical use. The SDI Vector One database indicated that, in 2008, the number of prescriptions was 38 million, so our rough estimate of 30% diversion suggests that about 11.4 million prescriptions might have been diverted to nonmedical use in 2008. This estimate is plausible based on the 2008 National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration, 2009), which indicates that a relatively high percentage of the U.S. population over 12 years of age (i.e., 8.5%) has a history of nonmedical use of prescription stimulants.

We recognize that many factors exist that may render our estimate of the number of individuals using stimulants an overestimate as well as an underestimate. The daily dose taken by the children who continue with medical use in the long-term is higher than the values defined by the INCB (30 mg/day for MPH and 15 mg/day for AMP). For example, Molina et al. (2009) reported that 24% of the ADHD cases in the multimodal treatment study of ADHD (MTA) who were taking medication at the end of the 14-month randomized clinical trial phase (at an average daily dose of 31 mg) were still taking medication eight years after baseline, but the dose had increased to 43 mg/day. Higher actual daily doses would contribute to an overestimate the number of individuals that could be treated by national supply specified by S-DDD. On the other hand, the operational definition of S-DDD assumes that individuals take medication 365 days per year, but weekend and/or summer drug holidays are common in clinical practice. Also, adherence to prescribed medication regimes is low. For example, Marcus and Durkin (2011) estimated that adherence (even allowing for drug holidays) was present in only 18.6% of the grading periods during the school year, so that, for many individuals, the medical use of stimulants is far fewer than 365 days per year. This fact would operate to reduce the S-DDD value and increase the number of individuals that could be treated with a given national supply. Potential inaccuracies were recognized by the INCB, so the qualifying term *for statistical purposes* was added to the original operational definition of DDD, which is now listed as S-DDD.

Does the Medical Use of Stimulants Improve Cognition?

A large number of controlled studies have documented that the medical use of stimulants improves both the behavior of children with ADHD and their performance on many laboratory tests of attention, with the former effect larger than the latter (e.g., Conners, 2002). A review of the recent literature on adults with ADHD indicates that the effects of medical use of stimulants are similar to those in children (Faraone & Glatt, 2010). Pietrzak, Mollica, Maruff, and Snyder (2006) reviewed the literature on double-blind evaluation of cognitive effects of medical use of stimulants in children with ADHD and concluded that about 65% of the studies reported significant stimulant-related improvement. In the Smith and Farah (2011) review of a smaller but substantial literature on cognitive enhancement

through nonmedical use, the authors concluded that, on some tasks, there were small average benefits but that the pattern is not clear (e.g., small beneficial effects across most individuals or large beneficial effects only in a few individuals, both of which result in small average effects). Also, controlled studies have produced null results as often as statistically significant results. Because most (but not all) of the studies of medical use have been with children, whereas all but a few studies of nonmedical use have been with adults, this comparison of medical and nonmedical use of stimulants runs the risk of confounding age with medical condition. Even so, in controlled research studies, improvements in attention caused by the medical use of stimulants in the treatment of ADHD (primarily in children) are substantially greater than those caused by nonmedical use of stimulants by individuals in the non-ADHD population (primarily adults). However, in a series of studies of adults with and without ADHD, we used positron emission tomography imaging to evaluate the neurotransmitter dopamine and its involvement in brain networks involved in motivation as well as attention. In stimulant-naïve adults with ADHD, we documented deficits (i.e., lower than normal density of the dopamine transporter and lower than normal availability of dopamine D2/3 receptors) in key components of a motivation network (i.e., the nucleus accumbens) as well as an attention network (i.e., the caudate nucleus), suggesting that ADHD might be as much a motivation deficit as an attention deficit (Volkow et al., 2009). In both ADHD and non-ADHD adults, the stimulant drug MPH blocks the dopamine transporter and increased dopamine at the synapse, and on cognitive tasks that may be mundane (e.g., working simple mathematical problems), this neural effect is associated with increases in subjective estimates of salience even for such a dull task (see Volkow et al., 2004). On the basis of this, the cognitive effects of nonmedical and medical use appear to reflect increased motivation as well as attention, which may alter interpretations of what aspects of cognition are enhanced by stimulants.

Smith and Farah's (2011) concept of nonmedical use of smart pills is in distinction to the use of stimulants as "awake pills," "diet pills," or "fun pills"; they contended that most nonmedical use is intended to improve academic performance (see Desantis & Hane, 2010; Teter, McCabe, LaGrange, Cranford, & Boyd, 2006). However, they did not discuss whether medical use improves academic performance. Most early studies of treatment of children with ADHD utilized rather insensitive, global tests of achievement and too-short periods of medication to yield positive benefits, so academic enhancement was not recommended as an expected benefit of medical use of stimulants (see Swanson et al., 1993). A recent 8- to 12-week trial reached the same conclusion (Hellwig-Brida, Daseking, Keller, Peterman, & Goldbeck, 2011). However, in the 14-month randomized clinical trial of pharmacological and non-pharmacological interventions in the MTA, the combination of stimulant medication and behavioral treatment produced a greater benefit on reading achievement than behavioral treatment alone (MTA Cooperative Group, 1999). Also, in a 5-year investigation, Scheffler and colleagues (2009) did find a positive association between stimulant treatment and reading/math performance, at least during the initial period of treatment, among grade-school-age children. In a study of school records for students from 4 to 17 years of age, Barbaresi, Katusic, Colligan, Weaver, and Jacobsen (2007) reported no difference in reading achievement in ADHD students who were treated and untreated with stimulants, but within the treated group, the dose of stimulant medication and reading achievement showed a modest positive correlation (0.15). In terms of adults, the review of Advokat (2010) concluded that the medical use of stimulants in college students did not promote learning or academic achievement. Overall, it is still uncertain whether the medical use of stimulants enhances academic achievement.

What Aspects of Cognition Are Enhanced in Medical Use?

Swanson, Baler, and Volkow (2011) reviewed the literature on cognitive effects of medical use of stimulants and discussed how effects on performance on laboratory tests depended on the domains of cognition the tasks evaluated, as well as on the presence of an ADHD-related deficit on a specific task. A decade ago, the most prominent theories of ADHD were based on the concept of a specific underlying core deficit in executive function (Pennington & Ozonoff, 1996) and response inhibition (Barkley, 1997). These theories implied that these domains of cognition were obvious targets for the medical use of stimulant medication. However, based on our review of the past decade of research, we concluded that cognitive enhancement was more prominent on tasks without executive function components. Our conclusions are consistent with those of other recent reviews of medical use (e.g., Advokat, 2010).

To focus on possible cognitive enhancement in nonmedical use, Smith and Farah (2011) excluded from their review studies with measures confined to perceptual or motor abilities (e.g., studies of visual search, dichotic listening, or simple vigilance) and studies of motivation that could improve the quality and quantity of work despite a given, unchanged level of cognitive ability. Their review was restricted to controlled studies of effects of nonmedical use on four domains of function (learning and long-term memory, working memory, cognitive control, and other executive functions). They concluded that stimulant-related cognitive enhancement depended on the type of cognitive process evaluated. For learning, about 50% of the studies reported no benefit, and the other 50% reported positive effects that depended further on the nature of the learning task, with the largest enhancement apparent for long-term recall from declarative memory. For working memory, the overall effects were mixed, but cognitive enhancement may have been present in some individuals who had poor performance in the placebo condition. For cognitive control, there were more studies with nonsignificant than significant results. For other executive function tasks, more null than positive findings emerged.

Thus, similar to the effects of medical use, the review by Smith and Farah (2011) suggests that for nonmedical use, effects on executive function tasks are among the smallest across domains of cognition.

What Subgroups of Individuals May Benefit Most From the Medical Use?

The data to address this question are sparse. There is a large literature on the ADHD subtypes (combined, inattentive, and hyperactive-impulsive), but the differences are not substantial. It is possible that level of severity of symptoms may affect the clinical response to medical use of stimulants. For example, in a secondary analysis of the 14-month outcomes in the MTA, Santosh et al. (2005) contrasted response to stimulants in a subset of severe cases defined by rediagnosis of cases based on narrow criteria of the International Classification of Diseases (10th revision [ICD-10]; World Health Organization, 1994) for hyperkinetic disorder (HKD). Only 25% of the MTA sample met the narrow criteria for the diagnosis of HKD, even though the remaining 75% did meet the broad criteria of the Diagnostic and Statistical Manual of Mental Disorders (4th ed. [*DSM-IV*]; American Psychiatric Association, 1994) for ADHD-combined type. The ICD-defined HKD cases showed a larger relative benefit of stimulant medication over behavior modification. Also, in an example of a relevant study of adults referred to a clinic for assessment of ADHD, Turner, Blackwell, Dowson, McLean, and Sahakian (2005) used a battery of cognitive tests to determine response to MPH. The severity of ADHD symptoms varied across the referred individuals, so only some met the adult criteria for ADHD. The latter manifested a more pervasive benefit of MPH across tasks. On the basis of these examples, we speculate that the

overall benefits of medical use of stimulants in children as well as in adults may be largest for subgroups of individuals with severe manifestations of ADHD symptoms.

Smith and Farah (2011) reached similar conclusions about the effects of nonmedical use in the working memory and cognitive control domains of function. For the studies reviewed in these areas, they concluded that cognitive enhancements were largest for individuals with the highest ratings of ADHD-like behaviors or traits (e.g., impulsivity) or some evidence of a deficit (i.e., those with the poorest performance in the placebo condition). This pattern suggests a question about the participants in studies of nonmedical use of stimulants: Do the participants represent the full range of cases in the population versus a self-selected group that may have subthreshold but above average manifestation of ADHD-like behaviors?

In summary, (a) the supply of stimulants has been increasing linearly for decades with no indication of an asymptote, apparently driven by increases in demand for medical and nonmedical use; (b) the supply (estimate of potential use) and reported use on national surveys (estimate of actual use) are discrepant, suggesting diversion of about 30% to nonmedical use; (c) the number of prescriptions for medical use is high (38 million), and the number diverted to nonmedical use is correspondingly high (11.8 million); (d) for both medical and nonmedical use, average benefits of stimulants on specific tasks may appear to be small because individuals do not have beneficial effects on all tasks; (e) for both medical and nonmedical use, relative benefits may be smaller on tasks that have high demands on executive function than on tasks that have low demands on executive functions; and (f) the greatest cognitive enhancement may occur in individuals with the greatest severity of behaviors that underlie the symptoms of ADHD.

Justification of Medical Use Within the Categorical Diagnosis of ADHD

Stimulant medications are classified as Schedule II drugs, which require an approved indication for medical use with verified efficacy as well as safety. For stimulants, the indication is met by the categorical diagnoses of ADHD as defined by the *DSM-IV* criteria of the American Psychiatric Association or HKD as defined by ICD-10 criteria of the World Health Organization. As described above, however, there are very different policies and decision rules applied in different countries, which result in large cross-national differences in recognition rates of ADHD and supplies of stimulants intended for medical use. In our recent chapter in a book on neuroethics (Illes & Sahakian, 2011), we (Swanson, Wigal, et al., 2011) proposed that the distinction between medical and nonmedical use would be better addressed as a policy issue than a medical issue. From this perspective, answers to the key questions addressed by Smith and Farah (2011) about cognitive enhancement associated with medical and nonmedical use of stimulants may vary across countries and over time.

If responses to both medical and nonmedical use of stimulants depend on individual differences in the severity of behaviors underlying ADHD, a common measure of severity may be essential to use for an adequate comparison of these two types of use. The dimension of symptom severity of ADHD that is provided by the typical ADHD rating scale has a highly skewed (nonnormal) distribution in the population. By definition, most individuals (i.e., those without psychopathology) will receive the same score indicating absence of symptoms, even though there is considerable variability in these asymptomatic individuals (e.g., see Polderman et al., 2007).

We (Swanson et al., 2001; Swanson, Wigal, & Lakes, 2009; Swanson, Wigal, et al., 2011) proposed an alternative to measure the variability in the nonclinical population by making a simple change in the wording of the 18 symptom-based items on the ADHD rating scales and constructing the Strengths and Weaknesses of ADHD-Symptoms and Normal-Behavior (SWAN) rating scale. The *DSM-IV*-defined content of the 18 items was retained, but rather

than ask for a rating of a restricted range of weaknesses (i.e., the extremes of the behavior that produce impairment, usually on a 4-point scale from 0 = *Not at All* to 3 = *Very Much*), we requested a rating that represents an individual's placement across the entire range of behavior related to each item. We anchored the SWAN ratings at 0 (representing average behavior) and asked for ratings of weaknesses (degree of symptom presence reflecting psychopathology) from 1 to 3, and we allowed for ratings of strengths (opposites of symptoms) from -1 to -3. Several recent epidemiological studies (see reviews by Swanson et al., 2009; Swanson, Wigal, et al., 2011) have shown that SWAN ratings are approximately normally distributed in the population.

If the normal distribution provided by the SWAN is used to characterize the entire population, then severity of ADHD-like behavior could be used to evaluate cognitive enhancement associated with total use of stimulants—that is, for both medical and nonmedical use. We propose that the overall response to stimulants would be related to the sign (positive or negative) and magnitude of the SWAN rating, featuring (a) a tendency for a small or nonexistent response for the majority of individuals in the middle of the distribution of the underlying behavior (i.e., with a SWAN score near 0), (b) an increasing tendency for a cognitive benefit for the individuals who are placed on the extreme right of the distribution (i.e., for individuals with positive symptom ratings on the SWAN), and (c) a decreasing tendency for a cognitive benefit for the individuals who are placed to the extreme left (i.e., for individuals with negative ratings—the opposites of symptoms—on the SWAN).

In summary, to provide answers to questions posed by Smith and Farah (2011) about cognitive enhancement of nonmedical use of stimulants that apply across countries and over time, it seems necessary to define a standard criterion that separates medical from nonmedical use of stimulants. Because, in practice, the diagnostic criteria vary substantially by geography, custom, and era, the degree of differential cognitive enhancement associated with medical and nonmedical use of stimulants may be confounded with these factors. A continuous dimension describing the full range of behavior in the population that underlies the symptoms of ADHD may provide a way to evaluate the total response to stimulant medication rather than separate responses to medical and nonmedical use.

Concerns About Addiction to Stimulant Drugs

A major concern about the widespread nonmedical use of stimulant drugs is that some individuals may become addicted. Smith and Farah (2011) devoted only a few paragraphs to this important issue, but it has been addressed by others in more detail, including the former president of the INCB (see Ghodse, 2007) and in a recent comprehensive article by Berman et al. (2009). It was also addressed in a book published soon after the epidemic of nonmedical use that occurred 40 year ago (Grinspoon & Hedblom, 1975) as well as in a recent book proposing that society is on the cusp of another epidemic (Rasmussen, 2008). Testimony to the congressional hearing in 1972 by the Judiciary Committee on the topic of diversion and abuse of stimulants as pep pills or diet pills claimed that about 7 million individuals in the U.S.A. were receiving prescriptions for stimulants in the 1970s and that about 6.5% of the population over 14 years of age had used stimulants in the past month (see Rasmussen, 2008). The 2008 National Survey of Drug Use and Health (NSDUH; Substance Abuse and Mental Health Services Administration, 2009) suggested that these conditions are again present in the U.S.A.

The risk for addiction from nonmedical use is unclear. Rasmussen (2008) speculated that in 1970, about 10% of those engaged in nonmedical use of stimulants were dependent on them (about 1 million individuals) and that about 300,000 individuals in the U.S.A. were addicted to these prescription drugs. The analysis of the NSDUH data on nonmedical use by Kroutil

et al. (2006) suggests that one out of 20 individuals who engage in nonmedical use of stimulants meet the *DSM-IV* criteria for dependence and abuse. In 2002, they estimated that this would represent over 303,000 individuals in the U.S.A. If nonmedical use is increasing at the same rate as medical use, then this number may have more than doubled from 2002 to 2008. With a large base (that is, the non-ADHD component of the population of the U.S.A.), the number of individuals affected may be large even though the percentage affected is small.

Because the supply and prescriptions are increasing for adolescents and young adults (the age groups most likely to engage in nonmedical use), perhaps the lessons of history deserve more attention than general accounts provided in books (e.g., Grinspoon & Hedblom, 1975; Rasmussen, 2008). This process was initiated by Sahakian and Morein-Zamir (2007) in a provocative article in a prestigious scientific journal (*Nature*) that generated considerable discussion and debate. In letters to the editor, we participated in the debate and warned that stimulant drugs have abuse potential and that widespread nonmedical use may result in addiction in a subset of individuals (see Swanson & Volkow, 2008; Volkow & Swanson, 2008). The issues were summarized succinctly in *Scientific American* (Stix, 2009) in an article with a provocative title ("Turbocharging the Brain"). This article provided a scholarly review of medical and nonmedical use of stimulants, highlighted unanswered questions about these increasing practices, and described some new drugs that are under development as possible agents to enhance cognition. The recent article by Berman et al. (2009) reviewed the science related to potential adverse effects from nonmedical use of stimulants, including consideration of the pattern of dosing as well as the duration of dosing. We reiterate that it is crucially important to consider whether the rate of transition to abuse and dependence differs for medical and nonmedical use of stimulants.

The historical experiences outlined above suggest that for nonmedical use, a small but significant percentage of the individuals seeking and periodically using stimulants with the intention of cognitive enhancement will escalate to abuse and become dependent on stimulants. This figure is in contrast to medical use in the treatment of ADHD, in which the percentage of treated patients that transition to abuse and dependence is assumed to be negligible.

However, this difference in risk for abuse, dependence, and addiction for medical and nonmedical use of stimulants has not been rigorously evaluated. The small percentage of affected individuals makes this a difficult task that will require large-sample studies to evaluate. There are many issues that need to be considered to evaluate the hypothesis that there is a greater risk of addiction from nonmedical than medical use. First, the initiation of medical use of stimulants still occurs in childhood in most cases, whereas nonmedical use appears to be initiated in adolescence or early adulthood. In general, individuals who are exposed to drugs in adolescence appear to be at a greater risk for abuse and addiction than those exposed at other ages (see Grant & Dawson, 1997). Second, stimulant drugs are sought by the individuals who engage in nonmedical use, but typically for medical use, the ADHD individual does not seek the treatment. Instead, medical use is recommended by others, such as the parents or teachers of a child or a spouse or employer of an adult with ADHD (see Swanson & Volkow, 2009). This differential motivation may affect the potential for addiction. Third, the dosing of stimulants is different for medical use (daily) and nonmedical use (weekly to monthly). As discussed by Berman et al. (2009), the latter may predispose to dependence and abuse of stimulants while the former may not.

Summary

In our commentary, we have addressed three topics. First, using the six key questions defined by Smith and Farah (2011), we have contrasted the literatures on medical and nonmedical use of stimulants, identifying some similarities—including a positive relationship between severity of the underlying ADHD-like behaviors and the degree of benefit from use of stimulants, relative benefits that are small for tasks that have a high demand on executive functions, and uncertainty about intended benefits in academic achievement. Second, we have noted that the legal distinction between medical and nonmedical use of stimulants depends on the categorical diagnosis of ADHD and that the criteria for making a diagnosis vary substantially across countries and over time. This variation complicates answers to questions about differential cognitive enhancement in medical versus nonmedical use of stimulants. Finally, we have emphasized warnings about the nonmedical use based on the history of diversion and abuse of stimulants in the past. We highlight that this issue must be taken seriously to avoid an unfortunate repeat of this history.

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