Comparing the Abuse Potential of Methylphenidate Versus Other Stimulants: A Review of Available Evidence and Relevance to the ADHD Patient

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The use of psychostimulants to treat attention-deficit/hyperactivity disorder (ADHD) has been controversial for a number of reasons. In an effort to clarify the extent to which the psychostimulant methylphenidate has abuse potential, the existing published evidence has been reviewed and is summarized here, with an emphasis on delineating a number of related but independent issues that are often confused. Methylphenidate produces behavioral effects associated with abuse potential as assessed by traditional assays, but the relevance of this literature to the clinical use of the drug in the treatment of ADHD is ambiguous at best. Existing neuropharmacologic data suggest that methylphenidate has pharmacokinetic properties that reduce its abuse potential as compared with other stimulant drugs of abuse, such as cocaine. *(J Clin Psychiatry 2003;64[suppl 11]:14–18)*

The treatment of attention-deficit/hyperactivity disorder (ADHD) with psychostimulant medication has been a somewhat controversial subject.[1,2] Among critics' concerns is the fear that the use of stimulant medications to treat ADHD may play a role in the development of drug addiction.[3–6]

A number of questions are related to the extent to which clinical stimulant use may be associated with substance abuse, including the following:

- Does methylphenidate have the potential for abuse?
- Is methylphenidate abused by people with ADHD?
- What are the neuropharmacologic substrates of abuse potential of methylphenidate and other abuse stimulants?

To address these questions, this article reviews existing evidence pertaining to each of the issues with an emphasis, where data are available, on comparative information with other stimulant drugs of abuse, such as amphetamine and cocaine.

EMPIRICAL EVIDENCE FOR ABUSE POTENTIAL OF PSYCHOACTIVE SUBSTANCES

The assessment of the abuse potential of psychoactive substances has been studied by various methods and across many levels of analysis.[7] For example, the extent to which the chemical composition of a given substance is similar to known drugs of abuse suggests that it, too, may have abuse liability. Likewise, a drug's potential for abuse may be evaluated by studying its neuropharmacologic effects in the central nervous system. However, drug abuse is, at its endpoint, a behavioral phenomenon, and much of the work of assessing a substance's potential for abuse will therefore utilize dependent measures that are behavioral.[8]

Methodologies

The abuse liability of various psychoactive drugs has often been measured with 2 primary behavioral assays: drug reinforcement and subjective effects. Drug reinforcement is assessed in nonhuman species using self-administration procedures in which an animal has the opportunity to make some response (e.g., a lever press) for the contingent delivery of the drug (e.g., usually i.v.). Drugs that are abused by humans will reliably maintain self-administration in animals. The reinforcing effects of drugs are typically studied in humans by exposing subjects to oral administration of a drug and placebo under double-

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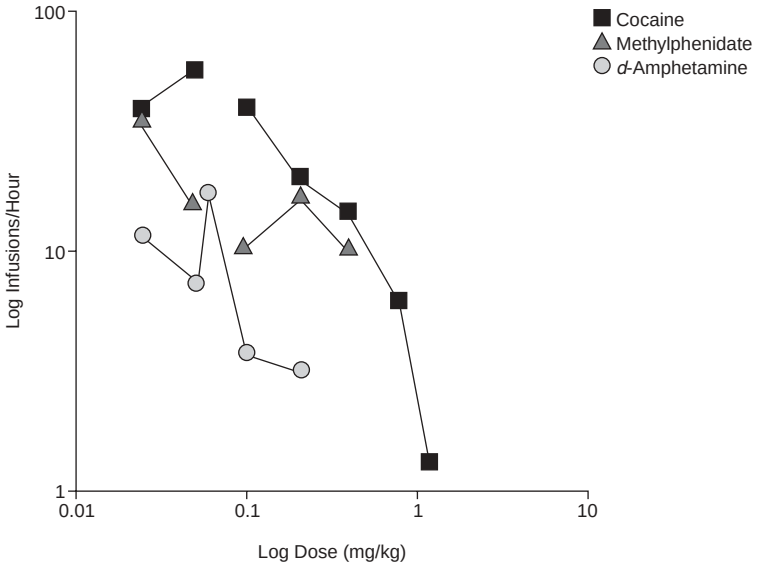
Figure 1. Reinforcing Effects of Methylphenidate: Nonhuman Studies[a]



[a]Reprinted with permission from Kollins et al.[8] Twelve studies were examined in which methylphenidate self-administration could be compared with self-administration of either *d*-amphetamine or cocaine. The figure shows comparative reinforcing efficacy across doses of the 3 compounds. All drugs were administered either i.v. or i.p.

blind conditions on separate days, thereafter permitting the subjects to choose which substance they wish to take. The reliable selection of the index drug over placebo is assumed to predict its abuse potential.[8]

Subjective effects of drugs are measured in human participants using a variety of measures, many of which are well-standardized (e.g., Addiction Research Center Inventory[9]). Other approaches to measuring subjective effects include adjective rating scales and visual analog scales. These kinds of measures produce reliable findings across drugs and drug classes and also predict which compounds are likely to be misused and abused outside of the laboratory setting.[10]

Abuse Potential of Methylphenidate

A review of the literature[8] identified a total of 12 studies of the reinforcing effects of methylphenidate in nonhuman subjects. In most of these studies, methylphenidate administered by injection was compared with either cocaine or *d*-amphetamine, also administered by injection. All 3 drugs exhibited comparable reinforcing effects, although the potency differed across the compounds. As expected, the rate of behavior decreased as a function of the dose that the animals received in each infusion (Figure 1).

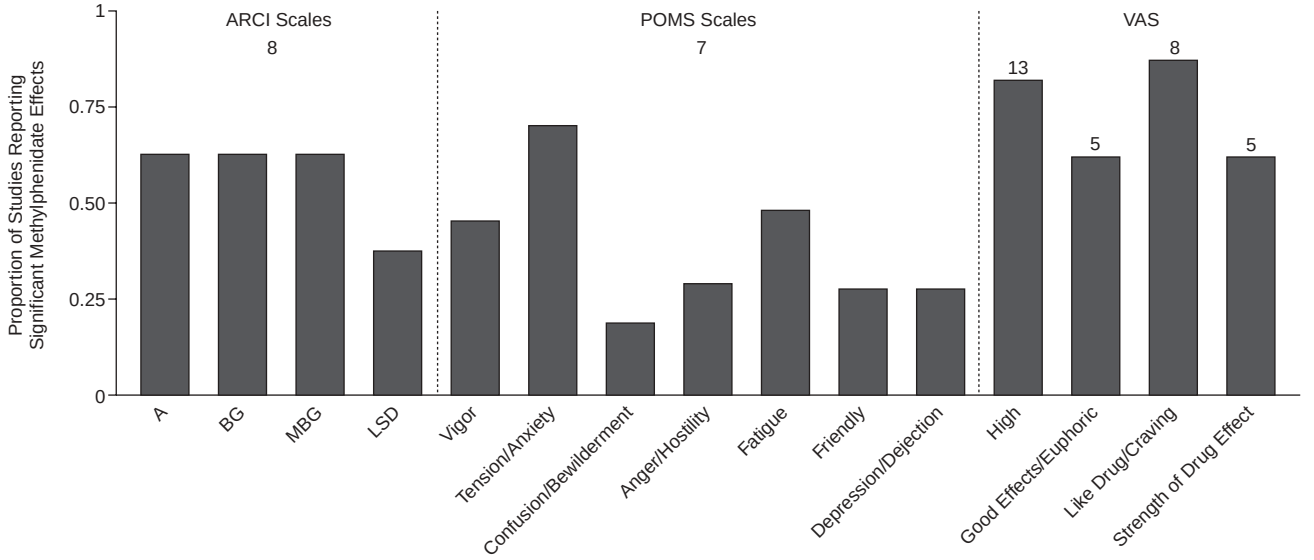
In 4 studies of the reinforcing effects of oral methylphenidate in humans, 2 demonstrated that under normal conditions, healthy adults did not choose methylphenidate significantly more than placebo, while the other 2 studies found some evidence of reinforcement, although 1 of these studies[11] reported that methylphenidate produced reinforcing effects only when the participants had been limited to 4 hours of sleep the previous night.[8]

The results of 25 studies evaluating self-reports of the subjective effects of methylphenidate suggested that it produces effects similar to those of *d*-amphetamine and produces overall effects consistent with abuse potential (Figure 2).[8] None of the studies providing support for the abuse potential of methylphenidate, however, were conducted with ADHD patients most likely to receive the drug for clinical purposes. Rather, the findings were obtained in other populations—healthy adults, stimulant abusers, psychiatric inpatients. As such, the question of whether individuals who are prescribed methylphenidate are likely to abuse the drug has not been directly addressed by this previous research. As will be described below, there is emerging evidence to suggest the abuse potential of methylphenidate may actually be lower in ADHD patients.

NEUROPHARMACOLOGIC BASIS FOR ABUSE POTENTIAL OF METHYLPHENIDATE

Because methylphenidate and cocaine share similar pharmacologic mechanisms, the comparative pharmacokinetics of the 2 drugs have been widely studied. In 1 study,[12] positron emission tomography (PET) was used to measure the temporal and spatial distribution of carbon 11 [^{11}C]-labeled methylphenidate, and results were compared with those for [^{11}C] cocaine in 8 healthy subjects. Analysis of the pharmacokinetic differences between methylpheni-

Figure 2. Subjective Effects of Methylphenidate: Human Studies[a]



[a]Reprinted with permission from Kollins et al.[8] Numbers above the columns specify the number of studies on which proportions were based for each instrument. The majority of human studies reviewed report significant effects of methylphenidate compared with placebo. Results were comparable to those for cocaine and *d*-amphetamine as well. The figure does not take into account route of administration or dose. Effects across studies, as expected, were dose dependent.

Abbreviations: A = amphetamine, ARCI = Addiction Research Center Inventory, BG = Benzedrine Group, LSD = lysergic acid diethylamide, MBG = Morphine Benzedrine Group, POMS = Profile of Mood States, VAS = visual analogue scales.

date and cocaine showed similarity between the drugs with regard to absolute levels binding to the dopamine transporter and initial uptake (when both drugs were administered i.v.). However, the rate at which methylphenidate was cleared from the brain was much slower than cocaine.[12]

It has been suggested that the initial fast uptake of methylphenidate or cocaine into the brain following i.v. administration very likely accounts for the subjective "high" reported by drug users. However, the relatively slow rate of clearance of methylphenidate from the brain may reduce the likelihood of repeated administration of drug to maintain a "high" that is typical of cocaine use. Figure 3[13] shows that, administered intravenously, methylphenidate enters the brain rapidly (8–10 minutes, similar to 4–6 minutes for cocaine) but has a relatively slow clearance, with a half-life of approximately 90 minutes versus 20 minutes for cocaine.[14] It is this difference that is thought to account for the fact that methylphenidate is much less abused than cocaine.[13]

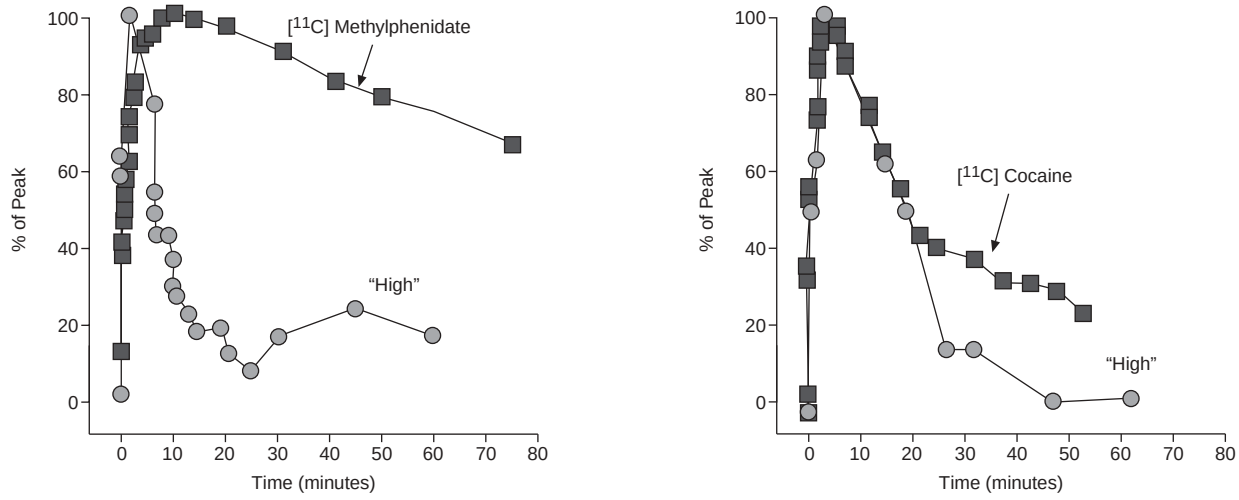
Oral Versus Intravenous Administration

The speed with which a drug is delivered to the brain is known to affect its reinforcing properties. This accounts for why drugs that are administered intravenously or inhaled are generally abused more often. With respect to methylphenidate, oral administration, the route exclusively used in clinical use, leads to slower rates of drug uptake compared with intravenous administration. Figure 4 shows peak concentration of [^{11}C] methylphenidate in the brain of a baboon at 8 to 10 minutes when administered intravenously, compared with a peak concentration at 60 to 120 minutes after oral administration.[13] As such, methylphenidate, like other drugs, has lower abuse potential when administered orally compared with other routes of administration. Moreover, there is evidence that extended-release formulations of methylphenidate have even lower potential for abuse than traditional formulations. For example, one study demonstrated that 20 and 40 mg of immediate-release methylphenidate were much more likely to produce significant subjective effects compared with placebo than the same doses of wax-matrix sustained-release methylphenidate.[15]

Dopamine Transporter Blockade

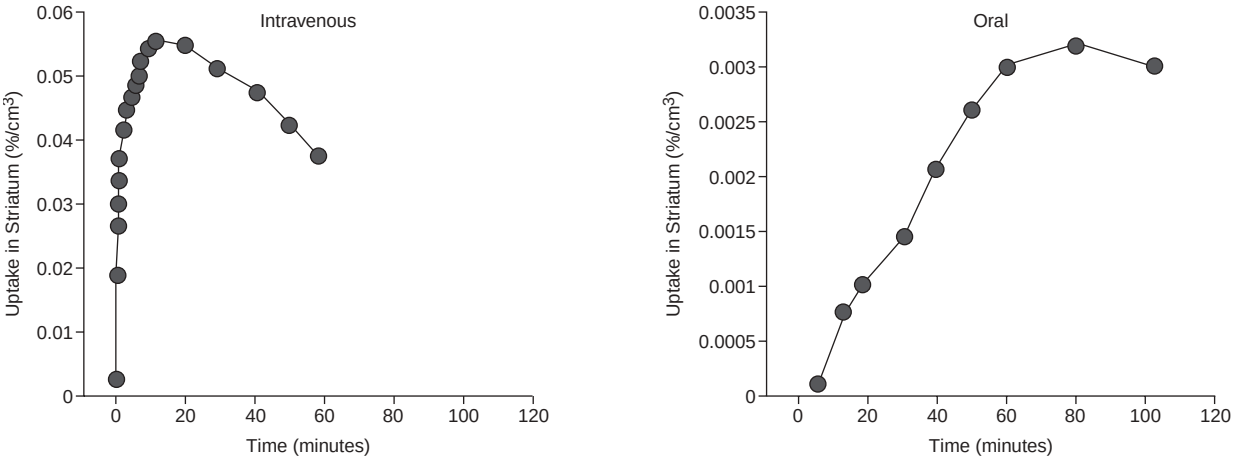
Methylphenidate is known to have high affinity for the dopamine transporter (DAT), an action hypothesized to be associated with mediating a drug's reinforcing effects and therefore its abuse potential. Even when administered orally at therapeutic doses, methylphenidate has been shown to occupy more than 50% of available DAT in relevant regions of the brain. Some studies, however, have shown that the occupancy of the DAT alone does not produce the characteristic stimulant "high" (e.g., Volkow et al.[16]), although other studies have found that oral doses as low as 20 mg produce significantly higher ratings of

Figure 3. Peak Concentrations of Methylphenidate Versus Cocaine[a]



[a]Reprinted with permission from Volkow et al.[13]

Figure 4. Clearance Rates of Methylphenidate: Intravenous Versus Oral[a]



[a]Reprinted with permission from Volkow et al.[13]

stimulant effects than placebo (e.g., Kollins et al.[15]). Insofar as the abuse potential of stimulant drugs is related to the action at the DAT, methylphenidate may actually have less potential for abuse in patients diagnosed with ADHD than in non-ADHD individuals. Recent imaging data suggest that patients with ADHD have a significantly higher density of the DAT in their brains than nondiagnosed individuals[17,18] and this very likely impacts the kinds of stimulant effects therapeutic doses of methylphenidate exert. As noted previously, studies documenting the abuse potential of methylphenidate have generally not been conducted in samples of individuals with ADHD. This finding is also consistent with anecdotal reports from clinicians who report that their ADHD patients rarely, if ever, indicate that they experience a drug "high" or other stimulant effects while taking methylphenidate.

SUMMARY

Under certain conditions, methylphenidate has been shown to have abuse potential comparable to cocaine and *d*-amphetamine as assessed by traditional behavioral assays.

The samples used in these studies, however, limit the interpretation of the findings to ADHD patients prescribed methylphenidate for clinical purposes.

- Samples have largely been taken from either healthy or substance-abusing adults.

- Subjects studied to date have not included children with ADHD.

The dynamic action of methylphenidate at DAT may limit the extent to which the drug will be administered frequently, as in cocaine bingeing, because the clearance of methylphenidate is much slower and uptake by way of oral administration is relatively slow.

A number of important areas remain to be studied with respect to the abuse potential of methylphenidate:

- The impact of brain development of children on abuse potential is unknown.
- Changes in dopamine system may result in age-related differences in DAT levels.
- The effect of previous stimulant exposure on abuse potential has not been systematically studied, although clinical experience has found that early stimulant exposure may have a protective effect.

In summary, methylphenidate has shown the potential for substance abuse in the laboratory setting. There is, however, virtually no evidence to date that the drug possesses significant abuse potential in patients who are likely to take the drug for clinical purposes. Future research should further clarify this potential difference in the drug's abuse potential to (1) assuage concerns about its misuse and abuse in individuals with ADHD and (2) increase understanding of potential neuropharmacologic differences between individuals with ADHD and nondiagnosed individuals.

Drug names: d-amphetamine (Adderall, Dextroamp, and others), methylphenidate (Ritalin, Concerta, and others).

Disclosure of off-label usage: Dr. Kollins has determined that, to the best of his knowledge, methylphenidate is not approved by the U.S. Food and Drug Administration for drug abuse liability assessment in healthy control adults.

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