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Assessing the abuse potential of methylphenidate in nonhuman and human subjects A review

Scott H. Kollins[a,*], Emily K. MacDonald[b], Craig R. Rush[c]

[a]*Department of Psychiatry, Duke University Medical Center, Box 3431, Durham, NC 27710, USA*
[b]*Department of Psychology, Western Michigan University, Kalamazoo, MI 49008, USA*
[c]*Departments of Behavioral Science, Psychiatry, and Psychology, University of Kentucky, Lexington, KY 40356-0086, USA*

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Abstract

Methylphenidate (MPH) is widely used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children, adolescents, and adults. Methylphenidate is clearly effective for the treatment of ADHD, but there is controversy as to whether it has significant abuse potential like other psychostimulants (e.g., D-amphetamine and cocaine). In general, the drug is believed to be abused at rates much lower than those for other stimulants. The present review examines studies that investigated the behavioral pharmacological profile of methylphenidate and discusses how results from these studies address its abuse liability. Using MEDLINE search terms methylphenidate, drug discrimination, reinforcement, self-administration, subjective effects, subject-rated effects, abuse potential, and abuse liability, along with a review of the references from identified articles, 60 studies were located in which the reinforcing, discriminative-stimulus, or subjective effects of methylphenidate were directly assessed in nonhumans or humans. Forty-eight (80.0%) of the studies reviewed indicate that methylphenidate either functions in a manner similar to D-amphetamine or cocaine (e.g., functions as a reinforcer, substitutes fully in drug discrimination experiments), or produces a pattern of subjective effects suggestive of abuse potential. The results are discussed as they pertain to factors that may account for the apparent discrepancy in abuse rates between methylphenidate and other stimulants, including characterization of actual abuse rates, defining abuse and misuse, pharmacokinetic factors, and validity of abuse liability assays.

Keywords: Methylphenidate; Drug abuse; Drug-discrimination; Drug reinforcement; Subjective effects

1. Introduction

Methylphenidate (MPH, Ritalin) is one of the most commonly prescribed psychoactive drugs in the United States (Cardinale, 1996). Clinically, it is used primarily in the management of Attention Deficit Hyperactivity Disorder (ADHD) and recent prevalence estimates suggest that between 6% and 7% of all school-aged children are prescribed the drug for such behavioral problems (Safer et al., 1996). Methylphenidate's efficacy has been documented for treating a range of behaviors across a variety of settings (Swanson et al., 1993). Despite its documented efficacy, questions have arisen regarding the potential misuse and abuse of this stimulant drug. A number of single-case studies exist in the literature describing intranasal or intravenous use of prescribed methylphenidate (Garland, 1998; Jaffe, 1991; Levine et al., 1986; Massello and Carpenter, 1999; Parran and Jasinski, 1991). Furthermore, there is evidence, primarily from nonscientific sources, that methylphenidate misuse and abuse may be widespread among adolescents and college students, with the drug garnering such street names as "Vitamin R," "Skippy," and "the smart drug"(Drug Enforcement Administration, 2000; Llana and Crismon, 1999; Stepp, 1996; Vogt, 1999).

Methylphenidate is a piperidine derivative structurally related to amphetamine. The neuropharmacologic profile of methylphenidate is similar to that of other commonly used or abused stimulants like cocaine (Hoffman and Lefkowitz, 1996). Methylphenidate, like cocaine, blocks the dopamine transporter (DAT) (Ritz et al., 1987). Methylphenidate and

* Corresponding author. Tel.: +1-919-416-2080.
E-mail address: kolli001@mc.duke.edu (S.H. Kollins).

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cocaine are very similar in terms of their actions at the DAT (Gatley et al., 1999; Volkow et al., 1999a, b). In baboons, for example, methylphenidate and cocaine produce comparable increases in synaptic dopamine levels (Volkow et al., 1999a). As another example, the in vivo potency of methylphenidate at the DAT is comparable to that of cocaine in human brain (Volkow et al., 1999b). In humans, the regional distribution of [^{11}C] methylphenidate is almost exactly the same as that of [^{11}C] cocaine (Volkow et al., 1995).

Because of its structural and pharmacological similarity to drugs such as cocaine and D-amphetamine, there is reason to suspect that methylphenidate may have significant abuse potential, and as a result, the drug has been regarded in conflicting ways by clinicians, scientists, and policymakers. One study that surveyed children and adolescents who had been prescribed methylphenidate found that nearly one in five had been approached to sell, give away, or trade their medication at least once in the past 5 years (Musser et al., 1998). The Drug Enforcement Administration (DEA) has recently expressed concern that diversion of methylphenidate and subsequent misuse is increasing in prevalence and have suggested that rises in methylphenidate production from 1768 kg in 1990 to 14 957 kg in 1999 have resulted in increased availability of the drug (Drug Enforcement Administration, 2000). Several indices of methylphenidate misuse have also steadily increased in the same time frame, such as the number of reported thefts from licensed handlers of the drug and the number of young people who have reported using it without a prescription (Drug Enforcement Administration, 1995; Feussner, 1998). In a recent testimony to the United States Congress, a DEA spokesperson cited information from case files and state investigative services suggesting that the drug has been illegally diverted in several ways, as evidenced by thefts of the drug from pharmacies and schools; ADHD "scams" in which parents obtain multiple prescriptions from different doctors and then use the drug illegally, sell, or trade it; undercover street sales; multistate distribution rings; multidrug distribution rings (along with cocaine and other substances); and smuggling from Mexico (Drug Enforcement Administration, 2000).

The data collection methods and reporting standards of the DEA have been criticized, however, and some have argued that the problem of methylphenidate misuse is not as alarming when base rates for prescriptions are considered. A number of empirical studies have also cast doubt on the notion that methylphenidate possesses significant abuse potential compared to other stimulants. For example, one study reported that despite comparable regional distribution patterns in the brain, intravenously administered methylphenidate was pharmacologically distinct from cocaine, particularly in the rate at which the drugs were cleared from the brain (Volkow et al., 1995). These authors concluded that this difference may account for the more prevalent abuse of cocaine as compared to methylphenidate (National Institute on Drug Abuse, Community Epidemiology Work Group (CEWG) 1995). Others have described reports of methylphenidate abuse in the literature as "anecdotal and uncommon" and have highlighted the discrepancy between the abuse potential and production of methylphenidate and the actual pattern and prevalence of its abuse (Cooper, 1998, p. 206).

Based on some of this controversy and the recent attention that methylphenidate has received, the purpose of the present paper is to evaluate the behavioral pharmacological profile of methylphenidate in both nonhumans and humans with an emphasis on those dependent measures that have traditionally been used to assess a drug's relative abuse potential: (1) the reinforcing effects, (2) the discriminative-stimulus effects, and (3) the subjective effects in humans. By reviewing this literature, the question of whether or not methylphenidate has the potential to be abused can be explicitly addressed. The behavioral pharmacological profile of a drug considered by itself, however, is not entirely predictive of drug misuse or abuse. Indeed, there are many factors beyond behavioral pharmacological properties that influence the likelihood that a substance will be abused, including biological and social determinants (Altmann et al., 1996). With such factors in mind, a comprehensive summary of the abuse potential of methylphenidate will allow for a critical analysis of the characteristics that contribute to its comparative abuse patterns with other similar drugs, especially cocaine and D-amphetamine.

We will first consider the relevance of the behavioral pharmacological profile of a drug in both nonhumans and humans as it pertains to the drug's abuse potential. Then, we will review research examining the reinforcing, discriminative-stimulus, and subjective effects of methylphenidate. Finally, we will discuss factors that may account for the relative abuse patterns of methylphenidate and other stimulants and suggest potentially important areas for future empirical work.

2. Assessing the abuse potential of drugs

An important component in the development, marketing, and ongoing clinical assessment of any psychoactive drug is a thorough evaluation of its potential for abuse and dependence. Decisions regarding the eventual approval of a drug and the manner in which it is controlled and prescribed are guided, to a large extent, by research targeting a drug's potential for abuse. The history of such abuse potential testing has been concisely reviewed elsewhere (Jaffe and Jaffe, 1989). The methods by which a drug's potential for abuse may be assessed are numerous and encompass several different levels of analysis, including chemical, pharmacological, and behavioral. At a chemical level of analysis, the extent to which a compound is structurally similar to known drugs of abuse is one index of abuse potential. At another

level of analysis, a drug's potential for abuse may be assessed by examining its pharmacodynamic effects in the central nervous system. For example, many commonly abused drugs (e.g., methamphetamine, cocaine, D-amphetamine) have been shown to increase synaptic levels of dopamine, albeit by different mechanisms. By contrast, drugs that are typically not abused by humans do not usually exert this effect on synaptic dopamine levels (Eshleman et al., 1994; Mach et al., 1997).

Arguably, drug abuse in humans is, at its endpoint, a behavioral phenomenon. Seeking and taking drugs are the events that cause the greatest amount of impairment, and these events are wholly describable in behavioral terms. Abuse liability assessments that use behavioral endpoints as dependent measures can be particularly informative with respect to the likelihood that, under a particular configuration of environmental conditions, a drug might be misused. The study of the interaction among drugs, other environmental stimuli, and behavior has defined the field of behavioral pharmacology and has generated a number of useful tools for assessing the abuse liability of drugs. From this tradition, three paradigms have been used extensively to assess the abuse potential of a wide range of drugs: reinforcing, discriminative-stimulus, and subjective effects.

The reinforcing effects of a drug may be the single most important determinant of its abuse potential since those drugs that function as reinforcers in laboratory animals are often abused by humans and, conversely, compounds not abused in humans are typically not self-administered in nonhuman species (Brady et al., 1987; Fischman and Mello, 1989). Preclinical studies with laboratory animals typically assess a drug's reinforcing effects by determining whether it maintains self-administration (Brady et al., 1990; Yokel, 1987). In a typical self-administration experiment, animals receive administrations (usually intravenous) of a drug or vehicle (i.e., placebo) contingent upon some response (e.g., a lever press). Drugs that maintain rates of self-administration greater than those observed with vehicle are reinforcers. For example, when cocaine is administered contingent upon some response requirement, the drug will maintain stable and high levels of responding in all species in which it has been examined (see LeSage et al., 1999 for a review).

Comparable procedures used with human participants have demonstrated that adult human subjects will emit responses at high rates for contingent administration of drugs, such as cocaine (e.g., Ward et al., 1997). An alternative method for assessing the reinforcing effects of drugs that is commonly used with human participants involves a choice procedure in which subjects are exposed to a drug and placebo under double-blind conditions on separate days (usually administered orally) and are then given the opportunity to choose which drug they wish to administer on subsequent days (de Wit and Johanson, 1987). With this procedure, the reliable selection of the capsule containing the drug (e.g., D-amphetamine) illustrates how the drug functions to reinforce the choice selection and is believed to predict the abuse potential of the drug under investigation (Johanson and Uhlenhuth, 1980).

The discriminative-stimulus effects of a drug help determine whether drugs share similar interoceptive effects and, as such, represent a second paradigm for assessing a drug's abuse potential. Preclinical laboratory studies characterize a drug's interoceptive or discriminative-stimulus effects using drug-discrimination procedures, in which one response (e.g., right lever press) is reinforced following the administration of a drug and a different response (e.g., left lever press) is reinforced following the administration of vehicle/placebo. Following training, novel drugs are administered to determine if they share discriminative-stimulus effects with the training drug (i.e., occasion similar response patterns). The drug-discrimination procedure has several advantages. First, drug discrimination is pharmacologically specific in that drugs from the same class as the training drug generally increase drug-appropriate responding as a function of dose, while drugs from different classes generally produce placebo-appropriate responding (Glennon et al., 1991). Second, results from drug-discrimination studies are generally concordant with drug action at the cellular level (Glennon and Young, 1987). Third, the discriminative-stimulus effects of drugs in laboratory animals are thought to be a model of the subjective effects of drugs in humans (Overton, 1987; Preston and Bigelow, 1991; Schuster and Johanson, 1988). Drugs that produce similar discriminative-stimulus effects in laboratory animals generally produce similar subjective effects in humans.

A final paradigm for assessing the abuse potential of a drug is by measuring its subjective effects in humans. A drug's subjective (or self-reported) effects are typically measured using standardized questionnaires and rating scales. The strength of these subjective effects is inferred from the difference between ratings before and after drug administration or after drug administration compared to placebo administration. The extent to which the drug effects are associated with subjective ratings of euphoria, drug-liking, or similarity to other drugs of abuse, is the extent to which the drug is believed to have abuse potential. Measures that have commonly been used to assess the subjective effects of drugs include the Addiction Research Center Inventory (ARCI; Martin et al., 1971) and the Profile of Mood States (POMS; McNair et al., 1971), which are standardized. Other studies have used investigator-constructed instruments, such as adjective rating scales and visual analog scales (e.g., Kollins et al., 1998a,b; Rush et al., 1998). Drug effects on all of these instruments tend to be dose dependent and pharmacologically specific. As such, subjective effects measured in this manner are believed to be strongly correlated with a drug's abuse potential (Jaffe and Jaffe, 1989; Jasinski and Henningfield, 1989).

As noted previously, the extent to which a drug exerts reinforcing, discriminative-stimulus, and subjective effects consistent with abuse potential is not itself the sole deter-

minant of whether a drug will be abused by humans in natural environments. The validity of these assays for predicting abuse potential has been debated previously (Fischman and Mello, 1989; Jasinski, 1977), and there are instances where drugs that predict abuse in laboratory evaluations are not abused and, conversely, drugs (or combinations of drugs) that are abused in humans that have never been evaluated or whose evaluation would not predict significant abuse (Brady and Lukas, 1984). For example, bupropion, a dopamine-uptake blocker used in the treatment of depression and nicotine dependence, exerts discriminative-stimulus (de la Garza and Johanson, 1987; Kamien and Woolverton, 1989) and reinforcing effects (Lamb and Griffiths, 1990), indicative of abuse potential in nonhuman species. Despite these obvious indicators, bupropion is not abused and does not exert similar discriminative-stimulus effects when evaluated in humans (e.g., Rush et al., 1998). These discrepancies warrant caution when interpreting the validity of the behavioral assays used to assess abuse potential. Nevertheless, these methods have generally been accepted as valid predictors of a drug's abuse potential and have been widely used for such purposes. For this reason, we will focus on these approaches in reviewing studies pertinent to methylphenidate's abuse potential.

3. Selection of studies for review

To select studies for review, we first performed a MEDLINE search using the following key terms, all in combination with the term "methylphenidate" and the Boolean operator "AND": self-administration, reinforcing effects, reinforcement, discriminative-stimulus effects, drug discrimination, subjective effects, subject-rated effects, abuse liability, and abuse potential. This initial search yielded 127 studies. At this point, studies from each search were examined for their relevance to assessing abuse liability as detailed below. We also scanned the references of the studies to identify additional citations that were not captured in the search.

3.1. Self-administration/drug reinforcement study selection

Studies identified using the reinforcing effects, reinforcement, and self-administration search terms were included if they met one of the following two criteria: (1) methylphenidate was tested directly to determine whether it would maintain self-administration behavior; or (2) some variant of the self-administration procedure was used to determine if methylphenidate would maintain other forms of behavior (e.g., choice procedures, progressive ratio procedures). Eight studies were identified that met the first criterion and seven studies were identified that met the second criterion for a total of 15 studies that assessed the reinforcing effects of methylphenidate.

3.2. Drug-discrimination study selection

Studies identified using the discriminative-stimulus effects and drug-discrimination search terms were included if they met one of the following two criteria: (1) either cocaine or D-amphetamine had been used as a training drug under standard drug discrimination procedures and methylphenidate had been used as substitution drug; or (2) a novel compound had been used as the training drug and methylphenidate, cocaine, and D-amphetamine had all been used as substitution drugs. Thirteen studies were identified which met the first criterion and seven studies were identified that met the second criterion, for a total of 20 drug discrimination studies.

3.3. Subjective effects/subject-rated effects study selection

Studies identified using the subjective effects, subject-rated effects, abuse liability, and abuse potential search terms were included if they met one of the following criteria: (1) methylphenidate was compared to either placebo or baseline on subject ratings of items designed specifically to assess abuse liability (e.g., POMS, ARCI, Visual Analog Scales); or (2) methylphenidate was compared directly to either cocaine or D-amphetamine on similar measures of abuse liability. Seventeen studies were identified that met the first criterion and eight studies were identified that met the second criterion for a total of 25 studies that assessed the subjective effects of methylphenidate. Six out of the eight studies that met the second criterion also met the first criterion, but were grouped separately for organizational purposes. One study that assessed the subjective effects of methylphenidate using the ARCI and the POMS in control and Parkinsonian subjects was not included in the review since it did not report statistics pertaining to main effects of the drug compared to placebo across subjective effects measures (Persico et al., 1998).

A total of 60 studies investigating the behavioral pharmacological profile of methylphenidate were reviewed. Worth noting is that these 60 studies represent only 53 published articles, because 7 of the studies were examined in more than one category. Three studies were reviewed as both drug discrimination studies and subjective effects studies (Heishman and Henningfield, 1991; Rush and Baker, in press; Rush et al., 1998), and four other studies were reviewed as both reinforcing effects studies and subjective effects studies (Chait, 1994; MacDonald and Kollins, 2000; Roehrs et al., 1999; Rush et al., in press).

4. Reinforcing effects of methylphenidate

4.1. Nonhuman studies

Eleven studies that examined the reinforcing effects of methylphenidate were conducted with nonhuman species

Table 1
Summary of studies investigating reinforcing/rewarding effects of methylphenidate

Study	Sample characteristics	*N*	Route	Methylphenidate dose range tested	Other drugs tested/dose range
Aigner and Balster, 1979	Rhesus monkeys	5	iv	0.01–1.0 mg/kg	Cocaine/0.03 mg/kg
Bergman et al., 1989	Squirrel monkeys	5	iv	0.01–0.3 mg/kg	Cocaine/0.03–0.30 mg/kg
Chait, 1994	Humans (healthy adults)	35	po	20–40 mg	D-amphetamine[a]
Collins et al., 1984	Rats	6	iv	0.32–1.0 mg/kg	Cocaine/0.32–1.80 mg/kg
Griffiths et al., 1975	Baboons	3	iv	0.1–0.8 mg/kg	Cocaine/0.4–1.6 mg/kg
Johanson and Schuster, 1975	Rhesus monkeys	13	iv	0.075–0.7 mg/kg	Cocaine/0.05–1.5 mg/kg
MacDonald and Kollins, 2000	Children with ADHD	5	po	10–30 mg	None
Martin-Iverson et al., 1985	Rats			2.5–5.0 mg/kg	D-amphetamine/1.5 mg/kg
Mithani et al., 1986	Rats	10	ip	5.0 mg/kg	None
Nielsen et al., 1983	Rat	4	iv	0.2–0.4 mg/kg	D-amphetamine/0.06 mg/kg
Risner and Jones, 1976	Dog	11	iv	0.2–0.4 mg/kg	D-amphetamine/0.05–0.10 mg/kg
Risner and Jones, 1975	Dog	12	iv	0.05–0.4 mg/kg	D-amphetamine/0.25–2.0 mg/kg
Roehrs et al., 1999	Humans (healthy adults)	6	po	10 mg	None
Rush et al., in press	Humans (healthy adults)	8	po	20–40 mg	D-amphetamine/10–20 mg
Wilson et al., 1971	Rhesus monkeys	8	iv	0.025–0.4 mg/kg	Cocaine/0.05–1.2 mg/kg

iv = intravenous; ip = intraperitoneally; po = oral.
[a] Chait (1994) reported comparisons to D-amphetamine from a previously published study.

(Table 1). In seven of these, methylphenidate self-administration was examined using traditional procedures, wherein an indwelling catheter was used to deliver contingent administration of methylphenidate following some learned response (Aigner and Balster, 1979; Bergman et al., 1989; Collins et al., 1984; Nielsen et al., 1983; Risner and Jones, 1975, 1976; Wilson et al., 1971). Two of the studies demonstrated that free access to either intravenous methylphenidate or D-amphetamine (for 4-h sessions or unlimited access over several weeks) resulted in dose-dependent self-administration of both drugs in dogs (Risner and Jones, 1975, 1976). Further, the patterns of self-administration were similar except for the fact that the relative potency of methylphenidate compared to D-amphetamine was 0.75 (Risner and Jones, 1976). Similarly, in a study with rats, 0.4 mg/kg intravenous methylphenidate resulted in response rates for contingent drug administration that were within approximately 10% of rates maintained by 0.06 mg/kg D-amphetamine (Nielsen et al., 1983). Four other studies provided comparative self-administration data for cocaine and methylphenidate. Three of these were conducted with nonhuman primates and demonstrated comparable rates of intravenous self-administration maintained by both drugs (Aigner and Balster, 1979; Bergman et al., 1989; Wilson et al., 1971). For example, one study reported the ED_{50} for cocaine and methylphenidate to be 0.05 and 0.04 mg/kg, respectively, for response rates maintained by intravenous drug infusions in primates (Bergman et al., 1989). Another study using rats demonstrated that 1.0 mg/kg intravenous methylphenidate maintained responding at rates significantly higher than saline and comparable to 1.0 mg/kg intravenous cocaine (Collins et al., 1984). Fig. 1 illustrates comparative self-administration data for cocaine, D-amphetamine, and methylphenidate and demonstrates the dose-dependent relation between drug dose and patterns of self-administration. All three drugs produced lower response rates as dose/infusion increased and the order of potency across studies was D-amphetamine > methylphenidate>cocaine.

Four additional studies with nonhuman participants (see Table 1) were identified that did not use standard self-administration procedures, but are still relevant to the reinforcing effects of methylphenidate (Griffiths et al., 1975; Johanson and Schuster, 1975; Martin-Iverson et al., 1985; Mithani et al., 1986). In the study most closely resembling standard self-administration procedures described above, intravenously administered methylphenidate (0.1–0.8 mg/kg) engendered high ratios of responding (ratios as high as 2400 responses each) in primates, although no saline comparison condition was reported (Griffiths et al., 1975). This study also demonstrated that, at equal doses,

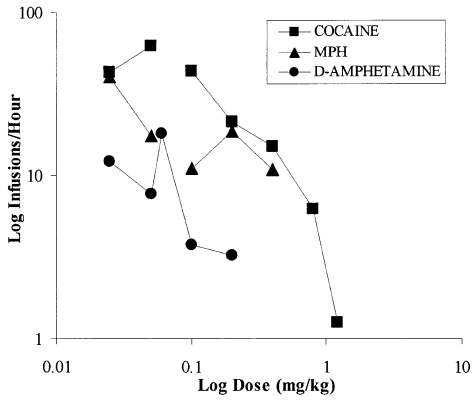

Fig. 1. Relative efficacy of methylphenidate, D-amphetamine, and cocaine for maintaining self-administration in nonhuman participants plotted in terms of infusions/hour as a function of dose (both axes plotted logarithmically). Each data point represents a reported mean from a single study or the mean of several reported means across studies. Data were adapted from Nielsen et al., 1983; Risner and Jones, 1975; and Wilson et al., 1971.

intravenous cocaine engendered higher response ratios than methylphenidate (e.g., 0.4 mg/kg maintained ratios of 4800 responses for cocaine and only 2400 for methylphenidate). Two studies with rats demonstrated that intraperitoneal methylphenidate (5.0 mg/kg) could reliably facilitate a conditioned place preference, a drug effect often equated with its rewarding properties (Martin-Iverson et al., 1985; Mithani et al., 1986). One of these studies reported that methylphenidate facilitated the acquisition of the place preference as readily as 1.5 mg/kg D-amphetamine (Mithani et al., 1986). Using a choice procedure, another study demonstrated that rhesus monkeys reliably chose intravenous methylphenidate (0.075, 0.2, 0.7 mg/kg) over saline injections more than 75% of the time (Johanson and Schuster, 1975). Moreover, this same study found that the highest dose of methylphenidate (0.7 mg/kg) was reliably chosen over cocaine (0.1, 0.5 mg/kg) in all tested animals ($N=4$).

4.2. Human studies

Four studies have been conducted to examine the reinforcing effects of orally administered methylphenidate in human participants. In the most clinically relevant of these studies, methylphenidate was selected more often (60% of the time) than either placebo (20%) or no capsules (20%) using a choice procedure in five children diagnosed with ADHD (MacDonald and Kollins, 2000). Although participants in this study received only one dose per individual, there was a clear dose-related increase in methylphenidate selection across participants from the lowest doses (10 mg chosen 50% of the time) to the highest dose (30 mg chosen 83% of the time). Another recent study with healthy adults used a progressive-ratio procedure similar to that used with nonhuman primates (Griffiths et al., 1975), and demonstrated that 40 mg oral methylphenidate (but not 20 mg) produced break points that were significantly higher than those produced with placebo and were comparable to 10 and 20 mg D-amphetamine (Rush et al., in press).

By contrast, two additional studies demonstrated that, under normal conditions, adult humans do not reliably choose to take methylphenidate (10–40 mg) over placebo or the option to take no capsules (Chait, 1994; Roehrs et al., 1999). However, when participants were limited to 4 h of sleep, 10 mg/kg methylphenidate was shown to be reliably selected (88%) over placebo (Roehrs et al., 1999). These findings stand in contrast to choice studies with nonhuman primates, wherein methylphenidate is reliably chosen over saline (Johanson and Schuster, 1975).

4.2.1. Summary

Thirteen of the 15 studies reviewed (86.7%) reported that methylphenidate either reliably maintained self-administration behavior, or was associated with other traditional measures of drug reinforcement or reward. Also, in 10 out of 11 studies for which comparative data were reported, the reinforcing effects of methylphenidate were generally similar to those of cocaine and D-amphetamine. Importantly, from the standpoint of abuse potential, the two studies in which methylphenidate failed to function as a reinforcer were conducted with human participants. One difference between these studies and the majority of nonhuman studies was the use of the oral route of administration. Since onset to drug effects has been demonstrated to be an important determinant of its reinforcing effects (e.g., Balster and Schuster, 1973), it is possible that this route of administration was the reason for a lack of reinforcing effects. Other methodological features of the studies, however, may also account for these discrepancies. One of these studies failing to report reinforcing effects for methylphenidate (Roehrs et al., 1999) used relatively low doses (10 mg), and also demonstrated that under conditions of sleep deprivation, methylphenidate was reliably chosen over placebo. Also, the one study that demonstrated a lack of reinforcing effects under all circumstances (Chait, 1994), also reported no statistically significant differences in the percentage of choices between methylphenidate and D-amphetamine, a stimulant with documented abuse potential, using the same procedures (cf. Chait, 1993).

5. Discriminative-stimulus effects of methylphenidate

5.1. Nonhuman studies

Seventeen of the twenty studies that assessed the discriminative-stimulus effects of methylphenidate were conducted with nonhuman species (Table 2). In 10 of these, either cocaine or D-amphetamine was used as the training drug and methylphenidate was examined as a substitution drug (Colpaert et al., 1979; de la Garza and Johanson, 1987; Emmett-Oglesby et al., 1983; Evans and Johanson, 1987; Huang and Ho, 1974; Kleven et al., 1999; McKenna and Ho, 1980; Rosen et al., 1985; Silverman and Ho, 1980; Wood and Emmett-Oglesby, 1988). Four of these studies demonstrated that 1.25–10 mg/kg cocaine administered either intraperitoneally or subcutaneously in rats could be reliably discriminated and that between 1.25 and 10 mg/kg methylphenidate substituted fully for the training drug stimulus (conventionally defined as >80% cocaine-appropriate responding or more than 80% of subjects tested identified methylphenidate as the training drug) (Colpaert et al., 1979; Emmett-Oglesby et al., 1983; Kleven et al., 1999; Wood and Emmett-Oglesby, 1988). One study that trained rats to discriminate 10 mg/kg cocaine from placebo reported that 2.5 mg/kg methylphenidate occasioned only 72% (±11%) cocaine-appropriate responding (McKenna and Ho, 1980), which is less than the conventional 80% criterion for full substitution. Five other studies demonstrated that 0.56–2.0 mg/kg D-amphetamine could be reliably discriminated and that 2.5–30 mg/kg methylphenidate fully substituted for the training drug stimulus (de la Garza

Table 2
Summary of studies investigating the discriminative-stimulus effects of methylphenidate

Study	Sample characteristics	*N*	Route	Training drug/dose	Methylphenidate dose range tested	Other drugs tested[a]/ dose range
Colpaert et al., 1979	Rats	7	sc	Cocaine/10 mg/kg	0.31–1.25 mg/kg	D-amphetamine/ 0.08–0.63 mg/kg
de la Garza and Johanson, 1987	Rhesus monkeys	4	ig	D-amphetamine/1.0 mg/kg	1.0–30.0 mg/kg	
Emmett-Oglesby et al., 1983	Rats	13	ip	Cocaine/1.25 mg/kg	10 mg/kg	D-amphetamine/ 0.02–0.64 mg/kg
Evans and Johanson, 1987	Pigeons	4	im	D-amphetamine/2.0 mg/kg	0.1–3.0 mg/kg	
Goudie et al., 1986	Rats	7	ip	DL-cathinone/2.0 mg/kg	0.5–4.0 mg/kg	Cocaine/1.25–10 mg/kg, D-amphetamine/ 0.25–1.0 mg/kg
Heishman and Henningfield, 1991	Humans (healthy adults)	8	po	D-amphetamine/30 mg	7.5–60 mg	
Huang and Ho, 1974	Rats	20	ip	D-amphetamine/0.8 mg/kg	0.5–2.5 mg/kg	Cocaine/7.5 mg/kg
Jones et al., 1980	Rats	6	ip	Bupropion/20 mg/kg	1.25–5.0 mg/kg	D-amphetamine/ 0.05–0.8 mg/kg
Kleven et al., 1999	Rats	20	ip	Cocaine/10 mg/kg	0.16–2.5 mg/kg	
McKenna and Ho, 1980	Rats	5	ip	Cocaine/10 mg/kg	2.5 mg/kg	D-amphetamine/ 0.25–0.5 mg/kg
Melia and Spealman, 1991	Squirrel monkeys	4	iv	GBR12909/1.0–1.8 mg/kg	0.01–0.30 mg/kg	Cocaine/0.03–1.0 mg/kg, D-amphetamine/ 0.01–.30 mg/kg
Rosen et al., 1985	Rats	4	ip	D-amphetamine/1.0 mg/kg	0.1–10.0 mg/kg	
Rush and Baker, in press	Humans (cocaine abusers)	16	po	Cocaine/150–200 mg	15–90 mg	
Rush et al., 1998	Humans (healthy adults)	5	po	D-amphetamine/20 mg	5–40 mg	
Shearman and Lal, 1979	Rats	14	ip	Pentylenetetrazol/20 mg/kg	2.5–10 mg/kg	Cocaine/5.0–20.0 mg/kg D-amphetamine/ 0.64–2.5 mg/kg
Silverman and Ho, 1980	Rats	11/15	ip	(+)amphetamine/1.0 mg/kg	2.5–5.0 mg/kg	
Tang and Franklin, 1987	Rats	5	sc	Apomorphine/0.1 mg/kg	1.0–10.0 mg/kg	Cocaine/3.0–30 mg/kg, D-amphetamine/ 0.1–3.0 mg/kg
Wood and Emmitt-Oglesby, 1988	Rats	8	ip	Cocaine/10 mg/kg	1.25–10.0 mg/kg	
Young and Glennon, 1998a	Rats	6	ip	(−)ephedrine/4 mg/kg	0.75–1.5 mg/kg	Cocaine/2.0–4.0 mg/kg, D-amphetamine/ 0.25–0.75 mg/kg
Young and Glennon, 1998b	Rats	5	ip	Methcathinone/0.5 mg/kg	0.5–1.5 mg/kg	Cocaine/0.5–3.5 mg/kg, D-amphetamine/ 0.1–0.5 mg/kg

ig = intragastric; ip = intraperitoneal; im = intramuscular; po = oral; iv = intravenous; sc = subcutaneous.
[a] Lists only whether the study also tested cocaine or D-amphetamine.

and Johanson, 1987; Evans and Johanson, 1987; Huang and Ho, 1974; Rosen et al., 1985; Silverman and Ho, 1980). These studies were conducted in a range of species (pigeons: Evans and Johanson, 1987; primates: de la Garza and Johanson, 1987; and rats: Huang and Ho, 1974; Rosen et al., 1985; Silverman and Ho, 1980), and across routes of administration (intraperitoneal: Huang and Ho, 1974; Rosen et al., 1985; Silverman and Ho, 1980; intramuscular: Evans and Johanson, 1987; and intragastric: de la Garza and Johanson, 1987).

Seven other studies were reviewed, in which a novel drug was used as the training drug and methylphenidate, D-amphetamine, and cocaine were examined as substitution drugs (see Table 2; DL-cathinone, Goudie et al., 1986; bupropion, Jones et al., 1980; GBR12909, Melia and Spealman, 1991; pentylenetetrazol, Shearman and Lal, 1979; apomorphine, Tang and Franklin, 1987; (−)ephedrine, Young and Glennon, 1998a; methcathinone, Young and Glennon, 1998b). In four studies with rats using the intraperitoneal route, all three drugs fully substituted for the training drug, albeit at different doses (Goudie et al., 1986; Jones et al., 1980; Young and Glennon, 1998a,b). The same pattern was observed in one other study using primates and the intravenous route of administration. One study demon-

strated that none of the three drugs substituted for the training drug in rats, although this study used the subcutaneous route of administration (Tang and Franklin, 1987). Finally, one study demonstrated that cocaine substituted for the training drug (pentylenetetrazol; Shearman and Lal, 1979), while no doses of either methylphenidate or (+) amphetamine did so.

5.2. Human studies

Three studies have examined the discriminative-stimulus effects of orally administered methylphenidate in human studies. D-amphetamine was used as a training drug in two of these and fixed doses of 30 and 20 mg D-amphetamine, respectively, were shown to be reliably discriminated (Heishman and Henningfield, 1991; Rush et al., 1998). In these studies, 20–60 mg methylphenidate fully substituted for the D-amphetamine training stimulus. One other study demonstrated that in cocaine abusers, 200 mg oral cocaine could be reliably discriminated from placebo, and that 15–90 mg methylphenidate dose-dependently increased cocaine-appropriate responding with the highest doses (60–90 mg) fully substituting for the training stimulus (Rush and Baker, in press).

5.2.1. Summary

To summarize the findings of the discriminative-stimulus effects of methylphenidate compared to cocaine and D-amphetamine, Fig. 2 graphically depicts the ratio of the minimum methylphenidate dose required to fully substitute (occasion >80% drug-appropriate responding) for a range of training doses of cocaine and D-amphetamine. In general, the ratio of the minimum dose of methylphenidate required to substitute fully for a cocaine training stimulus was less than 1 (range 0.125–8.0; median 0.275), indicating that in both rats and humans across a range of routes of administration (e.g., intraperitoneal, oral, subcutaneous), relatively lower doses of methylphenidate were identified as a cocaine-training stimulus. Methylphenidate was not as potent in substituting for the D-amphetamine training stimulus (range 1.0–53.7; median 3.125), but always fully substituted at some dose.

Overall, 18 out of 20 studies reviewed (90%) demonstrated that methylphenidate, cocaine, and D-amphetamine share discriminative-stimulus effects. Although findings from human and nonhuman studies are comparable, it appears that a number of factors influence the relative potency among these drugs in determining their shared discriminative-stimulus effects. For example, route of administration and species clearly affect the potency that methylphenidate exerts discriminative-stimulus effects similar to those of D-amphetamine. Intragastric administration in nonhuman primates (e.g., de la Garza and Johanson, 1987; see Fig. 2) resulted in much lower potency of methylphenidate as a substitution drug than oral administration in human participants (e.g., Rush et al., 1998). Also, studies with rodents using intraperitoneal administration resulted in potency levels

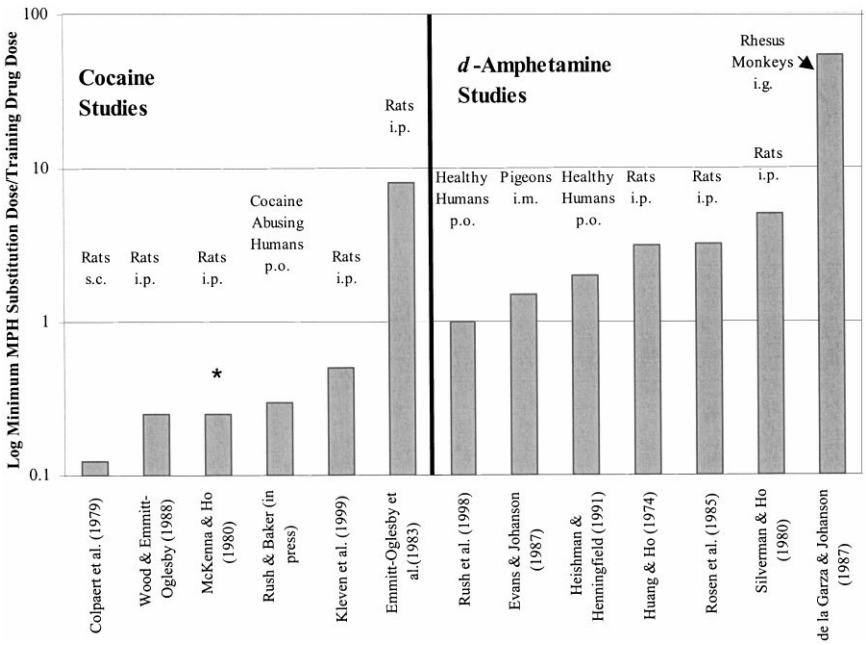

Fig. 2. Ratio of minimum substitution dose of methylphenidate (dose that resulted in at least 80% drug appropriate responding) to training dose of either cocaine or D-amphetamine used. Data are plotted on logarithmic coordinates. * Study reported that the highest dose of methylphenidate used (2.5 mg/kg) occasioned only 72% drug-appropriate responding for the training stimulus of 10 mg/kg. Species and route of administration for each study listed above each bar. ip = intraperitoneal; ig = intragastric; im = intramuscular; sc = subcutaneous; po = oral.

for methylphenidate as a substitution drug that were comparable to oral administration with human participants (e.g., Rush and Baker, in press; Wood and Emmett-Oglesby, 1988).

6. Subjective effects of methylphenidate

A total of 25 studies were identified that have investigated the subjective effects of methylphenidate in human

Table 3
Summary of studies investigating the subjective effects of methylphenidate

Study	Sample characteristics	*N*	Route	Subjective effects instrument(s) used	Methylphenidate dose range tested	Other drugs tested[1]/ dose range
Brown, 1977	Healthy adult males	17	po	MACL	10–20 mg	
Brown et al., 1978	Healthy adult males	59	po	MACL	10–20 mg	D-amphetamine/ 10–20 mg
Chait, 1994	Healthy adult males and females	35	po	ARCI, POMS, VAS	20–40 mg[2]	D-amphetamine[3]
Heishman and Henningfield, 1991	Adult males with significant drug use histories	8	po	ARCI, VAS	7.5–60 mg	D-amphetamine/ 3.75–30 mg
Huey et al., 1980	Psychiatric in-patients	8	iv	POMS, observations	0.5 mg/kg	
Kollins et al., 1998a	Healthy adult males and females	10	po	ARCI, POMS, VAS	20–40 mg each immediate and sustained release	
Kollins et al., 1998b	Children diagnosed with ADHD	8	po	ARCI[4]	2–30 mg[5]	
MacDonald and Kollins, 2000	Children diagnosed with ADHD	5	po	ARCI,[4] POMS, VAS		
Martin et al., 1971	Male prisoners incarcerated for crimes associated with drug use	12	sc	ARCI	15–60 mg/70 kg	D-amphetamine/ 7.5–30 mg/70 kg
Miller et al., 1988	Males diagnosed with alcohol dependence	17	po	POMS	10–20 mg	
Roache et al., 2000	Adult male and female cocaine abusers	57/12	po	ARCI, POMS, VAS	20 mg sustained release/5–60 mg immediate release	
Roehrs et al., 1999	Healthy adult males and females	6	po	ARCI, POMS	10 mg	
Rush and Baker, in press	Adult male cocaine abusers		po			Cocaine/50–300 mg
Rush et al., in press	Healthy adult males and females	8	po	ARCI, DEQ	20–40 mg	D-amphetamine/ 10–20 mg
Rush et al., 1998	Healthy adult males and females	5	po	ARCI, POMS, VAS	5–40 mg	D-amphetamine/ 2.5–20 mg
Smith and Davis, 1977	Healthy adult males and females	16	po	POMS	10–20 g	D-amphetamine/ 10–20 mg
Volkow et al., 1995	Healthy adult males	8	iv	VAS	0.5 mg/kg	
Volkow et al., 1996	Healthy adult males	4	iv	VAS	0.5 mg/kg	
Volkow et al., 1997	Adult males diagnosed with cocaine dependence, healthy controls	46	iv	VAS	0.5 mg/kg	
Volkow et al., 1998	Healthy adult males	16	iv	VAS	0.25–0.5 mg/kg	
Volkow et al., 1999c	Healthy adult males and females	8	iv	VAS	0.05–0.5 mg/kg	
Volkow et al., 1999d	Adult males diagnosed with cocaine abuse	20	iv	VAS	0.25–0.5 mg/kg	
Volkow et al., 1999f	Healthy adult males and females	14	iv	VAS	0.025–0.5 mg/kg	
Volkow et al., 1999e	Healthy adult males	23	iv	VAS	0.5 mg/kg	
Walker et al., 1988	Children diagnosed with ADHD	18	po	POMS	0.3–0.7 mg/kg	

po = oral; iv = intravenous; sc = subcutaneous.
[1] Lists only whether the study also tested cocaine or D-amphetamine.
[2] Only one dose tested cocaine or D-amphetamine.
[3] Compared to participants in another study. Not a within subject comparison.
[4] Only selected items from the ARCI were used in an experimenter-constructed questionnaire.
[5] Dose ranges varied across participants.

participants (see Table 3). Of the seven studies reporting comparative data on methylphenidate and D-amphetamine, all reported that methylphenidate alone significantly increased subjective effects on POMS scales (e.g., Chait, 1994; Smith and Davis, 1977), ARCI subscales (e.g., Chait, 1994; Heishman and Henningfield, 1991; Martin et al., 1971; Rush and Baker, in press; Rush et al., 1998), VAS scales (e.g., Chait, 1994; Heishman and Henningfield, 1991; Rush et al., 1998), and other scales (Modified Adjective Checklist, Brown et al., 1978; Drug Effect Questionnaire, Rush and Baker, in press) in orally administered doses ranging from 10 mg (Smith and Davis, 1977) to 90 mg (Rush and Baker, in press). Generally, these studies reported D-amphetamine to be more potent than methylphenidate in producing subjective effects (e.g., Martin et al., 1971; Smith and Davis, 1977), although the pattern of effects was similar across both drugs.

There were, however, exceptions to this pattern of findings. First, one study demonstrated that D-amphetamine produced significantly higher magnitude-subjective ratings on all of the following items compared to methylphenidate: ARCI Amphetamine, Benzedrine Group, Morphine–Benzedrine Group scales; VAS "drug liking," "stimulated," and "high" items (Chait, 1994). Another exception was from a study wherein 10 and 20 mg D-amphetamine produced significant changes in subjective effects associated with abuse potential (e.g., ARCI MBG scale, ratings of "high," "good effects") while methylphenidate did not produce effects that were different from placebo (Rush et al., in press). This same study, however, demonstrated similar patterns of effects for the two drugs for other subjective items, such as the ARCI A scale, and ratings of "like drug" and "willing to take again" (Rush et al., in press). Conversely, one study also reported that a high dose (60 mg) of methylphenidate produced ratings of VAS "high" that were significantly higher than placebo, while D-amphetamine failed to produce such results at any dose (2.5–30 mg; Heishman and Henningfield, 1991). Finally, one study that directly compared the subjective effects of oral cocaine (50–300 mg) and methylphenidate (15–90 mg) in human participants reported that methylphenidate and cocaine both dose-dependently increased ratings of "drug liking" and that methylphenidate was more potent (Rush and Baker, in press).

Studies that have assessed methylphenidate in the absence of a comparison drug have also found significant effects on subjective ratings. In a series of studies in which intravenous methylphenidate (0.25–0.5 mg/kg) was administered to adult participants, the drug consistently produced significant effects on the individual drug effect items of "high" and "rush" without negative stimulant effects, such as "anxious" and "restless" (Volkow et al., 1995, 1996, 1997, 1998, 1999c,d,f). Other studies using orally administered methylphenidate (10–40 mg) showed significant dose-dependent increases on a range of subjective measures (Brown, 1977; Kollins et al., 1998a; Roehrs et al., 1999).

Seven studies reported no statistically significant effects on any ARCI, POMS, or VAS scales traditionally associated with abuse potential (Huey et al., 1980; Kollins et al., 1998b; MacDonald and Kollins, 2000; Miller et al., 1988; Roache et al., 2000; Volkow et al., 1999e; Walker et al., 1988), although one of these reported significant methylphenidate effects on observer ratings of mania, euphoria, and arousal (Huey et al., 1980), and one reported a trend towards significant effects of methylphenidate on VAS ratings of "feel high" (Roache et al., 2000). For example, one study with hyperactive children reported that methylphenidate (0.7 mg/kg) reduced scores on the Anger/Hostility subscale of the POMS but produced no other significant results (Walker et al., 1988). Two other studies with ADHD children reported no effects of 5–30 mg methylphenidate on individual drug effect items or POMS scores (Kollins et al., 1998b; MacDonald and Kollins, 2000), and another study reported no effects in abstinent alcoholics (10–20 mg; Miller et al., 1988). Finally, in one study in which main effects for methylphenidate were not reported, 12/23 healthy control adults reported the overall effects of the drug to be "pleasant," versus 9/23 reporting "unpleasant" effects (Volkow et al., 1999e).

6.1. Summary

Fig. 3 summarizes some of the findings with respect to methylphenidate's subjective effects. A substantial proportion of all studies investigating the subjective effects of methylphenidate found significant effects for at least one dose of the drug compared to baseline or placebo conditions. Visual analog scales for the items "high" and "like drug/craving" were most often endorsed (84.6% and 87.5% of studies, respectively), while ARCI and POMS scales produced more varied results. Of the 25 studies reviewed which investigated the subjective effects of methylphenidate, 5 failed to report significant effects of methylphenidate in the expected direction on any of the dependent measures (Kollins et al., 1998b; MacDonald and Kollins, 2000; Miller et al., 1988; Roache et al., 2000; Walker et al., 1988), one study failed to demonstrate significant effects on one instrument (the POMS) despite significant effects on observer ratings (Huey et al., 1980), and one study (Volkow et al., 1999e) did not report overall group effects to determine if there was a main effect of methylphenidate on the subjective items tested. Overall, 18 out of 25 studies reviewed (72.0%) reported significant effects of at least one dose of methylphenidate on the subjective responses of participants.

Clearly, methodological features of these studies account for at least some of the discrepant findings. Three of the studies reporting no significant effects, compared to zero studies that did report significant effects, were conducted with children. Young participants may not have developed the verbal repertoire to accurately endorse the items associated with subjective drug effects (Kollins et al., 1998b;

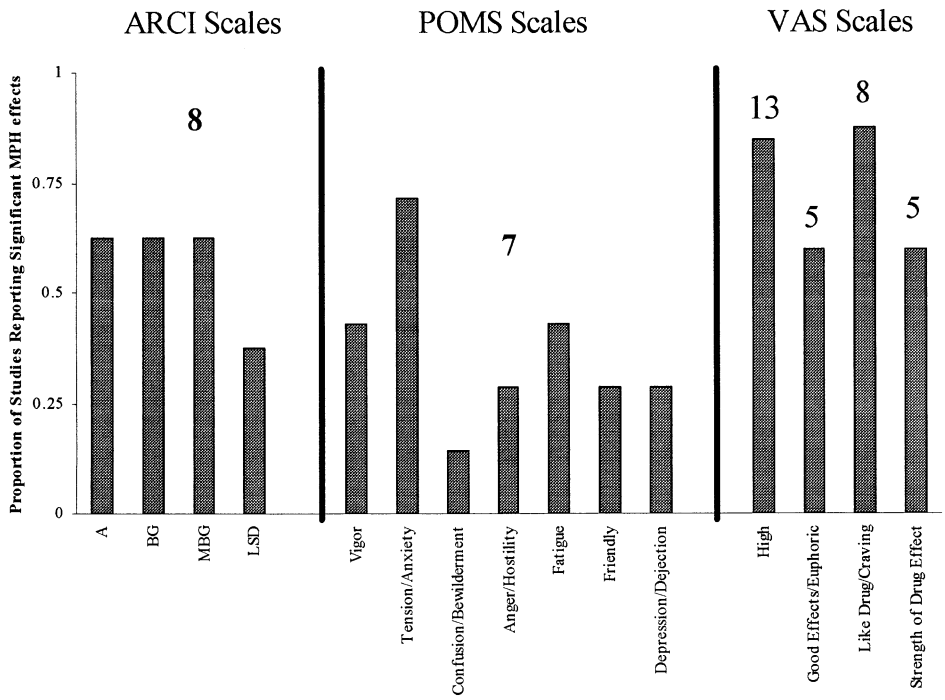

Fig. 3. Proportion of studies reporting significant effects for each of the scales and Visual Analog Scales compared to baseline or placebo measures. All effects reported in the figure were in the expected direction for stimulant drug effects. All studies reported increases under methylphenidate conditions compared to baseline or placebo, except for the "Fatigue" subscale of the POMS. The numbers above each bar indicate the number of studies on which the proportion is based. Proportions are based on eight studies for ARCI and seven studies for POMS scales.

Walker et al., 1988), although there were no effects for age in the 7–12-year-old children in one of these studies (Walker et al., 1988). Nevertheless, these findings are significant since they were obtained with the population most likely to receive the drug for clinical purposes. Another study that failed to demonstrate significant effects on POMS scores despite increases in observer ratings was conducted with psychiatric inpatients, who may have also been impaired in some manner relating to the reporting of subjective effects (Huey et al., 1980). One of the studies used a relatively low dose range of methylphenidate (10–20 mg) compared to other studies (Miller et al., 1988). Importantly, one of the studies that reported relatively weak effects of methylphenidate on indices of abuse potential was conducted with adults who were enrolled in outpatient treatment for cocaine dependence (Roache et al., 2000). This study also reported that orally administered methylphenidate (sustained release dose of 20 mg; immediate release doses 15–60 mg) had no effects on measures of cocaine craving. Finally, one study reported methylphenidate effects for at least a subset of individuals, but it was not clear from the analysis whether these effects resulted in group main effects (Volkow et al., 1999e). In general, the results from the studies examining the subjective effects of methylphenidate suggest that the drug functions similarly to D-amphetamine in producing subjective effects (no differences between the drugs in four out of five studies comparing them) and consistently produces a constellation of effects that is associated with abuse potential of the drug (see Fig. 3). These methylphenidate findings were obtained in different samples (healthy adults, stimulant abusers), across a range of doses (7.5–60 mg), and across routes of administration (e.g., intravenous, subcutaneous, oral).

7. Implications and directions for future research

Clearly, methylphenidate has a behavioral pharmacological profile similar to other abused stimulants. Overall, 48 out of 60 (80.0%) of the studies reviewed indicate that methylphenidate functions behaviorally in a manner similar to D-amphetamine or cocaine (i.e., produces comparable reinforcing, discriminative-stimulus, or subjective effects). These findings are neither novel nor surprising based on the neuropharmacological profile of the drug. Research, however, has failed to adequately explain the factors that account for the apparent discrepancy in actual abuse of cocaine, amphetamine, and methylphenidate. In the following paragraphs, we will call attention to several factors that may help differentiate the patterns of abuse and propose potentially important areas for future work. Specifically, we will address the accurate characterization of methylphenidate abuse, the distinction between diversion/misuse and abuse, pharmacokinetic differences among the stimulants, and the validity of abuse liability testing.

7.1. Actual rates of methylphenidate misuse/abuse

Despite the behavioral pharmacological profile of methylphenidate, it is generally accepted that the rates of methylphenidate abuse are minimal compared to those of cocaine or even D-amphetamine (National Institute on Drug Abuse, Community Epidemiology Work Group (CEWG), 1995). Future empirical work, however, needs to carefully substantiate these inclinations. A MEDLINE search we conducted turned up 20 case reports of methylphenidate abuse, almost all of which described intravenous route of administration with subsequent medical complications. Several other studies and reviews have reported methylphenidate abuse in specific groups of individuals (e.g., methadone maintenance patients, Raskind and Bradford, 1975), and in the general population (e.g., Crutchley and Temlett, 1999; Weiner, 2000). A recently compiled report from the Indiana Prevention Resource Center (IRPC) noted that 7.5% of Indiana high school seniors reported illicit use of methylphenidate in their lifetime (compared to 8.4% for cocaine use and 15.6% for amphetamine use; Indiana Resource Prevention Center, 1999). As noted previously, at least one study has reported that a substantial number of children have been approached to sell, trade, or give away their methylphenidate for recreational purposes (Musser et al., 1998). Also, popular press outlets have consistently reported problems with methylphenidate diversion over the past 3–5 years (e.g., Stepp, 1996; Student Net Publishing, LLP, 1998; Vogt, 1999).

Particular attention should be given to actual rates of misuse and abuse in individuals to whom the drug is most likely to be medically prescribed. The one published study of which we are aware that systematically measured both the discriminative-stimulus and subjective effects of methylphenidate in children diagnosed with ADHD noted an interesting discordance between these effects (Kollins et al., 1998b). Specifically, children in this study reliably learned a methylphenidate–placebo discrimination under some conditions but did not report reliable changes in subjective effects across the drug and placebo conditions (Kollins et al., 1998b). A recently completed study reported that children with ADHD chose methylphenidate 60% of the time (compared to 20% placebo and 20% neither) in a choice procedure and that selection of the drug increased monotonically with dose (MacDonald and Kollins, 2000). Future studies should investigate more specifically the developmental sequence of the reinforcing, discriminative, and subjective effects of methylphenidate and, perhaps, the relation of these effects to the clinical effects of the drug. Similarly, studies that examine the extent to which methylphenidate shares discriminative-stimulus and subjective effects with other stimulant drugs in children, such as D-amphetamine or caffeine, would be a useful addition to the literature for the same reasons.

Cocaine abusers are another group in which it would be important to clarify the behavioral pharmacological profile of methylphenidate, particularly in comparison to cocaine. Methylphenidate has been evaluated in several open-label trials as a pharmacotherapy for cocaine abuse (e.g., Grabowski et al., 1997; Levin et al., 1998; Roache et al., 2000) with somewhat mixed results. The comparable behavioral pharmacological profiles of cocaine and methylphenidate described in the present review should be taken into consideration when interpreting results from such studies. For example, it may be the case that, because of its pharmacological similarities, methylphenidate functions as putative "replacement" for cocaine without the concomitant "cravings" and abuse (Grabowski et al., 1997; Volkow et al., 1995). However, given the demonstrated similarities between these two drugs (albeit via oral administration, Rush and Baker, in press), significant caution is warranted for trials that attempt to substitute methylphenidate for cocaine. In such cases, use of sustained-release formulations of methylphenidate may be warranted given that this results in lower magnitude subjective effects (Grabowski et al., 1997; Kollins et al., 1998a).

7.2. Distinguishing between abuse and misuse/diversion

Another possible factor that may account for the discrepancy between methylphenidate abuse and that of cocaine or D-amphetamine has to do with the ways in which this particular behavior is characterized. By definition, substance abuse refers to the continued use of a drug that leads to significant impairment characterized by failure to fulfill important obligations, recurrent use under hazardous conditions, and legal and interpersonal problems (American Psychiatric Association, 1994). Although the case reports in the literature suggest that some individuals develop problems with methylphenidate use to this extent, much of the popular press and anecdotal information regarding nonmedical use of the drug centers on its use as a more mild stimulant. One review characterized this pattern of use in an effort to stay up later and "party" longer in college students, or in an effort to sharpen mental skills and study harder (Weiner, 2000). As such, it may be possible that the perception of low abuse liability is generated by the fact that the drug rarely leads to significant impairment. In any case, researchers and policymakers alike should consider the potential consequences of diversion/misuse of methylphenidate, even in cases where such use does not lead to actual patterns of substance abuse clinically defined.

Another way of characterizing misuse of methylphenidate as distinct from diagnosable substance abuse or dependence is by conceptualizing use of the drug as a means of gaining access to other forms of reinforcement or avoiding otherwise unpleasant consequences. One reviewed study, for example, demonstrated that under some environmental conditions (e.g., sleep deprivation), even low doses of methylphenidate are reliably chosen over placebo (Roehrs et al., 1999), possibly to increase alertness and improve functioning and/or to alleviate negative mood

states associated with fatigue. Similarly, the study wherein children with ADHD reliably chose methylphenidate over placebo or no capsules (MacDonald and Kollins, 2000) may be interpreted by considering that these children have a history of reinforcement in the form of academic productivity, teacher approval, etc. following medication administration. Finally, those anecdotal reports of methylphenidate use almost invariably involve the drug being used as an aid for some other form of potentially reinforcing activity (e.g., social interactions/"partying," work, studying, etc.). This approach for conceptualizing methylphenidate's abuse potential as compared to that of cocaine and D-amphetamine could be investigated by manipulating access to different kinds of reinforced activities and evaluating the extent to which methylphenidate is selected as a function of such access.

7.3. Pharmacokinetic differences

Pharmacokinetic differences between methylphenidate and other abused stimulants may also help account for differential patterns of abuse. Methylphenidate is most commonly available and administered in oral form, which, due to the rate of onset of effects, may limit its abuse liability compared to injected or insufflated forms of the other stimulants. The one study bearing on this issue demonstrated that a sustained-release formulation of methylphenidate, whose peak plasma levels are lower and, presumably, whose onset and offset of drug effects are subsequently slower (Birmaher et al., 1989), produced lower magnitude subjective effects compared to an immediate release formulation (Kollins et al., 1998a). A potential caveat to this argument, however, is that methylphenidate can be dissolved and injected (e.g., Parran and Jasinski, 1991). Thus, despite its most common commercially available oral form, the drug can be administered via routes that significantly influence pharmacokinetics and absorption rates.

The relevance of pharmacokinetics to differential abuse patterns has been addressed, to some extent, by the work of Volkow and colleagues (e.g., Volkow et al., 1995, 1997, 1999c,d,e,f). This work has suggested that, although methylphenidate and cocaine produce comparable levels of subjective reports (such as "high," and "rush"), and that these reports are correlated with plasma concentrations of the drug, methylphenidate is cleared from the brain much more slowly than cocaine (Volkow et al., 1995). According to Volkow and colleagues, these pharmacokinetic differences are associated with different levels of drug craving that are theoretically related to the extent to which an individual will subsequently seek out and self-administer the drug.

This important work provides a number of possibilities for further investigation into the differential abuse patterns of methylphenidate and cocaine. Specifically, it will be important to determine whether these pharmacokinetic differences correspond to actual reinforcing/self-administration behavior under laboratory conditions. Such work might be accomplished by utilizing choice methodology discussed previously (e.g., de Wit and Johanson, 1987) in the context of imaging studies similar to those conducted previously by Volkow and colleagues. As such, it would be possible to determine whether the specific pharmacokinetic differences between cocaine and methylphenidate translated into functional/behavioral differences in patterns of self-administration.

7.4. Validity of behavioral pharmacological assays

Approximately 80% of studies reviewed suggest that methylphenidate shares reinforcing, discriminative-stimulus, and subjective effects with other abused stimulants. This drug, however, is generally not regarded as an abuse problem. It could be argued that this discrepancy is the result of assays that are not valid or sensitive for predicting actual abuse. As noted previously, there are cases of drugs whose profile of effects in nonhumans does not predict comparable patterns of effects in human participants (e.g., bupropion, de la Garza and Johanson, 1987; Kamien and Woolverton, 1989; Lamb and Griffiths, 1990; Rush et al., 1998). Indeed a smaller proportion of studies conducted with humans (23/32, 71.8%) support the assertion that methylphenidate shares the same abuse potential as cocaine and D-amphetamine compared with nonhuman studies (25/28, 89.3%). It could be the case, for example, that other factors not measured by these procedures are more valid or sensitive for predicting actual abuse of a drug, such as pharmacokinetic activity (e.g., Volkow et al., 1995, see above). The fact remains, however, that even in human studies, there is evidence that methylphenidate is similar to cocaine and D-amphetamine (e.g., Rush and Baker, in press; Rush et al., 1998; Rush et al., in press). Since there are few other compounds that exhibit the same profile of abuse potential in laboratory studies with human participants that are not misused or abused, it seems unlikely that the validity or sensitivity of these assays is a sufficient explanation for the discrepancy in abuse rates of methylphenidate versus other stimulants.

More work that uses these assays in human participants will be important to further clarify the relative abuse potential among the stimulant drugs. For example, only four studies to date have investigated the reinforcing effects of methylphenidate in human subjects (Chait, 1994; MacDonald and Kollins, 2000; Roehrs et al., 1999; Rush et al., in press). To the extent that the reinforcing effects of a drug are considered to be one of the most powerful predictors of abuse, future research should strive to delineate the extent to which methylphenidate exerts reinforcing effects in human participants across a range of doses. Choice procedures similar to those used in the previously published studies should be extended to within-subjects designs in the same manner as studies of drug choice with other compounds

(Chait, 1994; de Wit and Johanson, 1987). Alternatively, experimental designs that can help determine the relative reinforcing effects of methylphenidate and other stimulants would also represent a substantial contribution to the literature. For example, further use of the progressive ratio schedule arrangement might help clarify the extent to which methylphenidate produces reinforcing effects at higher doses and in comparison to D-amphetamine and/or cocaine (e.g., Rush et al., in press).

Additional research is also needed to clarify the discriminative-stimulus effects of methylphenidate alone and in comparison with other stimulant drugs of abuse in human studies. Our review revealed that no substitution studies conducted with adult human participants have used methylphenidate as the training drug. Furthermore, clarifying the manner in which methylphenidate can come to control discriminative responding will offer insight into how likely it will be misused. Similarly, the extent to which methylphenidate shares discriminative-stimulus effects with D-amphetamine and cocaine needs to be studied in greater detail. One recent study (Rush and Baker, in press) provides data that are consistent with the preclinical finding that methylphenidate substitutes for cocaine in drug-discrimination procedures (Wood and Emmett-Oglesby, 1988). Other human studies that utilize similar methods to compare methylphenidate and cocaine will provide important information regarding relative abuse potential. For example, a novel-response procedure (e.g., Smith and Bickel, 1999), in which an additional response alternative representing a "not sure" or "neither" option is added to the traditional drug discrimination procedure, could be used to investigate the comparative discriminative-stimulus effects of methylphenidate. Such a procedure would help characterize more precisely how similar methylphenidate is to a cocaine- or D-amphetamine-training cue.

Further studying the reinforcing and discriminative-stimulus effects of methylphenidate in humans serves at least three important purposes. First, it adds information to our growing knowledge base regarding the extent to which methylphenidate shares stimulus properties with cocaine and D-amphetamine. Second, such research would fill an important comparative gap in the literature by extending findings from preclinical studies to human populations. Finally, this work will help evaluate the validity of these assays for assessing the abuse potential of methylphenidate and other compounds.

8. Summary and conclusions

The present review highlights the similarities between methylphenidate and the commonly abused stimulants, cocaine and D-amphetamine. Although the behavioral pharmacological profile of these drugs is very similar, the actual rates of abuse are believed to be much lower for methylphenidate. However, what little data exist on the actual prevalence rates of methylphenidate and other stimulant abuse suggest that this issue may be in question (e.g., Indiana Resource Prevention Center, 1999). We have highlighted a number of potentially informative research questions that may help clarify the relative abuse potential of methylphenidate and other stimulants as well as the actual patterns of misuse and abuse. In any case, the results of the present review suggest that methylphenidate, even in typically administered oral form, is not benign with respect to abuse potential. The bulk of laboratory studies support this in human participants, and the magnitude of subjective ratings does not appear to be heavily impacted by route of administration. As such, physicians should exercise caution in clinical decision making about when to use the medication. Moreover, those individuals overseeing its administration (parents, school officials, etc.) need to be alert to the potential for its diversion and misuse. This caution should, of course, be weighed against the well-documented clinical benefits of the drug for many children, adolescents, and adults. It is hoped that future research in this area will clarify more specifically those neuropharmacological and behavioral factors that contribute to the abuse of methylphenidate and other stimulants.

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