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ORIGINAL INVESTIGATION

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Assessing methylphenidate preference in ADHD patients using a choice procedure

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Abstract *Rationale:* Methylphenidate (MPH) is widely used in the treatment of attention deficit hyperactivity disorder (ADHD) and is associated with positive clinical effects across a wide range of domains. Despite the clinical effectiveness of MPH, concern has arisen with respect to its abuse potential. *Objectives:* To assess MPH preference in adults diagnosed with ADHD using a choice procedure and to evaluate the relationship among drug preference, therapeutic efficacy, and abuse potential in a clinical sample. *Methods:* Participants were ten volunteers (ages 18–22 years) with ADHD who were receiving MPH treatment. Preference was assessed using a double-blind choice procedure with four sampling sessions wherein subjects received either placebo or MPH and eight choice sessions when they chose either capsule or no capsules. *Results:* Overall, MPH was chosen significantly more often than placebo (χ^2=52.5; P<0.001) and participants were equally separated into groups of those who chose MPH reliably (MPH choosers) and those who did not (MPH non-choosers). MPH decreased ADHD symptoms and resulted in lower ratings of stimulant effects among MPH choosers. MPH choosers also reported higher levels of baseline ADHD symptoms. *Conclusions:* Despite higher preference of MPH than placebo in this clinical sample, other measures of abuse potential were not elevated, and MPH choosers were more symptomatic than non-choosers. As such, MPH preference in ADHD populations likely reflects therapeutic efficacy rather than abuse potential. Future work should examine MPH choice in diagnosed and non-diagnosed populations to further explore the role of clinical efficacy in the preference of this stimulant drug.

Keywords Methylphenidate · ADHD · Drug preference · Reinforcing effects · Abuse potential

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Introduction

Attention deficit hyperactivity disorder (ADHD) functionally impairs 3–5% of the school-age population (American Psychiatric Association 1994), and the persistence of ADHD into adolescence and adulthood has been widely supported (Barkley 1990; Biederman et al. 1993; Gittelman et al. 1985; Wilens et al. 1995). Most individuals with ADHD receive pharmacological treatment, and the majority of products prescribed for ADHD are methylphenidate (MPH) based (Robinson et al. 1999; Zarin et al. 1998; Zito et al. 2000). In children with ADHD, MPH-based products have positive effects across a wide range of domains (DuPaul et al. 1998; Greenhill 1998). Similarly, in adults diagnosed with ADHD, MPH is associated with improvements in attention span, behavior, cognitive aptitude, memory processing, mood stability, and sensorimotor coordination (Faraone et al. 2004; Spencer et al. 1995).

Despite the clinical effectiveness of MPH, concern has arisen with respect to its abuse potential (see Kollins et al. 2001 for review; Drug Enforcement Administration 2000; Llana and Crismon 1999; Safer 2000; Safer et al. 1996; Popper 1995). For example, in a survey of school-aged children, one of six reported having been approached to buy, sell, or trade MPH (Musser et al. 1998). MPH misuse has also been reported in adolescents in outpatient substance-abuse treatment programs, and in non-clinical samples of college students (Babcock and Bryne 2000; Marsh et al. 2000). Case reports document more clinically significant patterns of MPH misuse, with users taking the drug to induce euphoria by crushing the tablet and administering it intranasally or intravenously (Fulton and

Yates 1988; Jaffe 1991; Parran and Jasinski 1991). Thus, the misuse and diversion of MPH has been documented and may be increasing.

In addition to survey-based research, laboratory studies suggest that MPH functions behaviorally like other stimulant drugs of abuse, such as *d*-amphetamine and cocaine, in non-humans and humans. In relation to these other stimulants, MPH produces comparable discriminative stimulus, subjective, and reinforcing effects (Kollins 2003; Kollins et al. 2001).

Traditionally, the reinforcing effects of a drug are considered to be one of the most powerful predictors of abuse because of the face valid nature of the assays used to assess these effects and because of the close correspondence between reinforcing effects and other measures of abuse potential (Balster and Bigelow 2003; Fischman 1989). To date, however, only four published studies have directly examined the reinforcing effects of MPH in humans and results have been mixed. Two studies assessed the reinforcing effects of MPH using a choice procedure in healthy adult participants. One of these reported that MPH was chosen on only 27.6% of choices, compared with 8.6% for placebo and 63.8% for no capsules at all (Chait 1994); while the other study reported that 10 mg MPH was reliably chosen more often than placebo, but only when participants were sleep deprived (Roehrs et al. 1999). Two additional studies reported that MPH administered either orally or intranasally produced dose-dependent reinforcing effects in healthy adults using two different assays (progressive ratio procedure, Rush et al. 2001; multiple choice procedure, Stoops et al. 2003).

No studies have experimentally assessed the abuse potential of MPH in individuals with ADHD who are prescribed the drug for clinical purposes. In fact, only a few studies have examined the reinforcing effects of psychoactive drugs in individuals who receive them for clinical purposes. For example, the reinforcing effects of diazepam and alprazolam—sedatives which have clearly demonstrated abuse potential in non-clinical samples (Gomez et al. 2002; Juergens 1991; Woods and Winger 1995)—have been examined in individuals diagnosed with varying levels of clinically significant anxiety (McCracken et al. 1990; Roache et al. 1997; deWit et al. 1986). In one study, volunteers with either generalized anxiety disorder or panic disorder preferred alprazolam significantly more than placebo under free-choice, double-blind conditions, which by definition suggested reinforcing effects. The patterns of self-administration and subjective effects, however, were not suggestive of misuse or abuse potential in this study (Roache et al. 1997). The implication of this study is that, in clinical samples, the reinforcing effects of a drug may be more associated with therapeutic efficacy than with the potential for abuse, and that the examination of both subjective effects and reinforcing effects is necessary to make this important distinction.

In the past decade, the therapeutic use of MPH has increased, leading to debates surrounding the prescription rates and safety of this stimulant drug (Rappley 1997). Critics argue that MPH is overprescribed (see Safer 2000 for a discussion) and that early stimulant treatment predisposes individuals with ADHD to develop problems with substance abuse (Lambert and Hartsough 1998). Although mounting evidence suggests the opposite to be true (i.e., that stimulant treatment for ADHD serves a protective function for the development of substance use disorders; Wilens et al. 2003), the reinforcing effects of MPH have yet to be studied in a sample of patients for whom the medication is known to have clinical benefits. The purpose of the present study was to examine MPH preference and participant-rated effects in adults diagnosed with ADHD so as to more clearly distinguish the drug's therapeutic efficacy from its abuse potential in this clinical sample to whom it is most commonly administered.

Materials and methods

Participants

Participants in this study were seven males and three females (ages 18–22 years). The participants were recruited through local physicians and psychologists, recruitment flyers, and word of mouth on the basis of two criteria: (a) an established diagnosis of ADHD and (b) a current prescription for MPH for the treatment of symptoms associated with ADHD. All participants had been receiving MPH treatment for at least 6 months prior to selection for the study. At the time of the study, all subjects were receiving immediate-release MPH. One subject had been on an extended release formulation several years prior to the study, but had been on immediate-release MPH for the 6 months prior to the study.

To corroborate the ADHD diagnostic status of participants and to ensure a homogeneous group, participants were required to receive a score of 36 or higher on the Wender Utah rating scale (WURS; Ward et al. 1993) and obtain a *T* score of 65 or higher on the ADHD symptoms scale of the Conners Adult ADHD Rating Scale (CAARS; Conners et al. 1999b). Patients were instructed to complete the questionnaires based on their behavior when they were not on their medication. Both of these instruments have been shown to have adequate psychometric properties and have good predictive validity at identifying adults who meet full criteria for ADHD (Conners et al. 1999a; McCann et al. 2000; Stein et al. 1995; Ward et al. 1993). In addition, all volunteers had been previously diagnosed by pediatricians, family physicians and/or counselors, and had been receiving stimulant medication for years. The primary care physicians for each volunteer also reviewed the protocol and approved their participation.

Participants were excluded if they were taking any other type of psychoactive medication, exhibited any gross neurological, sensory or motor impairment, had a history of other significant learning or psychiatric problems, or any current severe psychiatric disturbances (e.g., suicidality, homicidality, criminality). A total of 17 individuals were screened and seven were excluded for the following reasons: not currently receiving MPH treatment (four participants), not willing to receive placebo (two participants), did not meet inclusion criteria on the CAARS (one participant). The ten individuals who completed the study had a mean CAARS ADHD total subscale *T* score of 77.9 (range 67–90), a mean WURS total score of 54.6 (range 36–63), and were receiving a mean maintenance dose of 16.5 mg MPH (range 10–30 mg).

Participants received monetary compensation for their participation in the 13 sessions. Participants received US $5 for each session and an additional US $20 for completing all 13 sessions. In addition, by returning their daily questionnaires, participants were entered into weekly drawings for the opportunity to win gift certificates and coupons to local businesses and restaurants. The Human Subjects Institutional Review Board at Western Michigan University approved this work.

Procedure

Volunteers participated in 13 sessions. The first session was a screening session wherein the participant completed self-report assessment measures. In addition, medical history, comorbid mental health diagnoses, length of time on MPH, and dosing information were obtained. None of the participants reported comorbid psychiatric diagnoses.

Each participant's maintenance dose of MPH and an inert placebo were administered in opaque capsules (size 01). Placebo and MPH capsules were placed in separate bottles labeled as "Bottle A" and "Bottle B." Participants were instructed that they would receive either their typical dose of MPH or placebo throughout the experiment. They were also instructed that, after taking their capsules, they would be free to leave the laboratory and resume their daily activities. Participants were instructed to complete questionnaires provided to them, 1.5 h and 4 h after leaving the laboratory, to be returned by the end of the day. During sampling sessions, participants were provided one capsule of either MPH or placebo. During choice sessions, participants were presented with both MPH and placebo capsules—along with a choice of no capsules—and were instructed to select one of the three possible options.

For experimental sessions, participants were asked to maintain their normal caffeine and nicotine use and to refrain from eating 1 h before the session. In addition, participants were asked to refrain from taking their MPH prescription for at least 4 h prior to coming into the laboratory. In general, participants chose to schedule their sessions first thing in the morning, so they refrained from taking their first dose of MPH until they arrived at the session. The 4-h restriction on their medication administration did not deviate significantly from their typical medication regimen.

There were three sessions each week for 4 weeks. The methods used in the present study are modeled after similar drug preference studies (Chait et al. 1987; deWit et al. 1984; Johanson et al. 1983; Johanson and Uhlenhuth 1982).

Sampling sessions

The first four sessions were sampling sessions. The sampling sessions were designed to allow participants to experience the effects of the two drug conditions (MPH and placebo) on the basis of which they would subsequently make their drug choice.

On the first sampling day, upon arriving at the laboratory, participants were given a standard light snack (juice and breakfast bar). Participants then completed the participant-rated effects scale (PRES). During the first sampling session, after completing the participant-rated effects questionnaire, participants received either placebo or MPH in a capsule labeled "Pill A" or "Pill B." In the second sampling session, participants received the other substance in a capsule labeled with the other letter. Participants also received a card labeled with the same letter as the pill administered as a reminder of which capsule they received that day. Participants were instructed to associate the effects of the capsule with its letter label. Capsule letter assignments varied across participants, and the order in which placebo and MPH were scheduled in the sampling sessions was counterbalanced across subjects and within subjects across weeks. The third and fourth sampling sessions followed the same capsule administration order.

After receiving the capsule, the participants were free to leave the laboratory and resume daily activities. Previous studies examining the reinforcing effects of drugs in clinical samples have used similar outpatient procedures whereby the participants make their drug choices in the context of their everyday lives (Roache et al. 1997). Volunteers were given two questionnaire packets and were instructed to complete them in 1.5 h and 4 h following capsule ingestion. Because these participants had demanding class and work schedules, in addition to being diagnosed with ADHD, they were asked to complete questionnaires only twice post-drug administration so as to minimize interference with their daily functioning. Participants were required to return their packets to the laboratory by 1700 hours, at which time they received their ticket for the weekly drawings. To increase compliance, participants were asked to record the time of questionnaire completion and were required to return the questionnaires to the lab 4 h post-drug administration.

Choice sessions

The remaining eight sessions were choice sessions. In the choice sessions, following the completion of questionnaires, participants were presented three cups for the drug choice administration: one labeled "Pill A" (or whatever letter corresponded to MPH), one labeled "Pill B" (or whatever letter corresponded to placebo), and an empty cup labeled "C." The participant chose either to ingest "Pill A," to ingest "Pill B," or to take neither capsule. The use of a "neither" option was included to replicate prior studies of the reinforcing effects of MPH (Chait 1994) and to provide a more reliable measure of the reinforcing efficacy of the chosen substance (Spiga and Roache 1997). This choice procedure is a technique that has been used to measure the reinforcing effects of a number of different drugs, in a range of contexts and with various subject populations (deWit and Griffiths 1991; Foltin and Fischman 1991; Johanson and deWit 1989). Following each choice, the participant was presented with the appropriate letter-matched card. After capsule administration, the participant was free to leave the laboratory and resume daily activities. The procedures for collecting participant-rated effect questionnaires were identical to those used in the sampling sessions.

Dependent measures

Drug preference

Drug choice was the primary measure of drug preference. The number of times one option (MPH, placebo, neither) was chosen over the other served as an indicator of its relative reinforcing effects.

Participant-rated effects

The participant-rated effects were assessed pre-drug administration, 1.5 h and 4 h post-drug administration. The participant-rated effects measures are as follows.

Participant-rated effects scale (PRES) The PRES is a 25-item scale developed for this study to assess the subjective effects of MPH in adults diagnosed with ADHD. Items on this form were derived from four primary sources: Addiction Research Center Inventory (ARCI; Martin et al. 1971), Profile of Mood States (POMS, McNair et al. 1971), CAARS (Conners et al. 1999b), and the DSM-IV (American Psychiatric Association 1994). Items included those that had been used to measure the participant-rated effects of many drugs and are sensitive to the effects of stimulants (Heishman and Henningfield 1991). The items from the CAARS and the DSM-IV included symptoms of ADHD and were selected because of clinical utility in determining the effects of stimulant medications in this population.

Items from the questionnaire were rated on a five-point scale (1–5), where each numeric value corresponded to a phrase describing the frequency or intensity of the item (1, not at all; 2, a little bit; 3, moderately; 4, quite a bit; 5, extremely). Participants were instructed to rate each item according to how they felt "at that moment."

End of the day questionnaire This five-item questionnaire was administered approximately 4 h after capsule ingestion to measure the overall effect of the drug received. Participants rated "drug strength," "drug liking," "good effects," "bad effects," and "like to take again" on a five-point scale (0, not at all; 1, a little bit; 2,

moderately; 3, quite a bit; 4, very much). Participants were also prompted to provide reasons for their pill choice, and to report any untoward drug effects.

Perceived effectiveness Participants were asked prior to the study to rate how effective their current prescription of MPH was for them. Ratings were made on a five-point scale that was anchored with the points 1="not effective" and 5="extremely effective."

Data analysis

Drug preference The number of times MPH, placebo, and neither were chosen were taken as indicators of participant drug preference and can be conceptualized as an index of the drug's positive reinforcing properties (deWit et al. 1984). The reinforcing effects of MPH were assessed by calculating the total number of choices of MPH, placebo, and neither across participants and examining the proportion of choices with a chi-square analysis. "Choosers" were defined as individuals who selected MPH on at least five of eight occasions. Choice patterns among "MPH choosers" and "non-choosers" were analyzed using independent *t*-tests.

Participant-rated effects The participant-rated effects were analyzed by transforming the 25-item questionnaire into three rationally derived composite scores: ADHD composite (10 items: unable to concentrate, focused*, forgetful, talkative, fidgety, distracted, restless, impulsive, overactive, inattentive), mood composite (12 items: happy*, anxious, tense, angry, sad, fatigued, annoyed, cheerful*, nervous, agitated, irritable, frustrated), and stimulant composite (3 items: hungry*, energetic, excited). The composite scores were averaged for each subject at each of the three time periods (pre, 1.5 h, 4 h). Separate averages were calculated for MPH and placebo sampling sessions, as well as for each of the three choices (MPH, placebo, neither) for choice sessions. Because participants were not exposed to the same number of MPH, placebo, and no-drug days, data from the choice days were not analyzed statistically (items marked with an asterisk were reverse scored).

Independent *t*-tests were used to assess the differences between subsequent MPH choosers and non-choosers with respect to pre-drug ADHD, mood, and stimulant composite scores. Pre-administration scores for both choosers and non-choosers were averaged across MPH and placebo sampling sessions to obtain a single baseline measure for each participant-rated effect composite. Data from the sampling sessions were also analyzed using a two-way analysis of variance (time×group) to compare the participant-rated effects obtained by MPH choosers and non-choosers prior to MPH administration and 1.5 h after administration. The end of day questionnaire ratings were analyzed using paired *t*-tests to compare ratings on each item following MPH and placebo across all sessions and separately across sampling and choice sessions. Given the small sample size and the exploratory nature of this study, we did not correct statistically for the multiple comparisons conducted and results should therefore be interpreted with caution.

Results

Reinforcing effects

The results of the choice sessions were analyzed by examining the percentage of MPH choices per subject (Fig. 1). Of 80 total choices across all participants (8 choices each), MPH was chosen 40 times (50%), placebo was chosen 26 times (32.5%), and neither was chosen 14 times (17.5%). A chi-square analysis found that the number of choices of MPH, placebo, and neither differed significantly (χ^2=52.5, P<0.001).

According to the criteria used by Chait (1994), participants 1, 3, 6, 7, and 10—on the experimental doses of 10 mg, 20 mg, 30 mg, 10 mg, and 20 mg, respectively—were classified as "MPH choosers." The remaining participants were classified as "non-choosers." Specifically, participants 2, 5, and 8—on experimental doses of 10 mg, 20 mg, and 10 mg, respectively—chose placebo more often than MPH, and participants 4 (experimental dose 20 mg) and 9 (experimental dose 20 mg) did not demonstrate reliable choice patterns (Fig. 2). Participants classified as choosers or non-choosers, however, still did not exhibit exclusive choice for one substance. MPH choosers selected MPH significantly more often than non-choosers (mean MPH choices for choosers=6.2, mean for non-choosers=1.8; t=5.0, P=0.001). Conversely, MPH choosers chose placebo significantly less often than non-choosers (mean placebo choices for choosers=0.6, mean for non-choosers=4.6; t=−3.6, P=0.007). There were no significant differences between MPH choosers and non-choosers with respect to choices of neither.

Participant-rated effects

An analysis of pre-drug scores revealed significant differences between non-choosers and MPH choosers only on the stimulant-effects composite (mean for choosers=8.35, mean for non-choosers=6.25; t=2.7, P=0.03).

Results from the two-way ANOVA also revealed a significant interaction (time×group) for the ADHD composite scores ($F_{1,8}$=9.0, P=0.017). There was a trend toward a significant interaction (time×group) for the stimulant drug effects ($F_{1,8}$=4.8, P=0.059), which likely results from the decrease in effects among MPH choosers. These effects are depicted graphically in Fig. 3.These results suggest that participants who reliably chose MPH reported a significant decrease in ADHD symptoms and a trend toward a significant decrease in stimulant drug

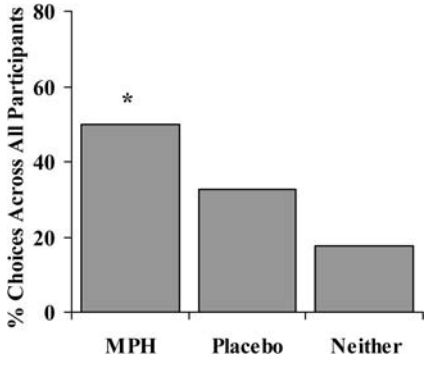

Fig. 1 Percentage of choices for methylphenidate (MPH), placebo, and neither across all participants (N=10). *Asterisk* indicates that the total number of MPH choices across participants was significantly different from choices of placebo and neither (χ^2=52.5, P<0.001)

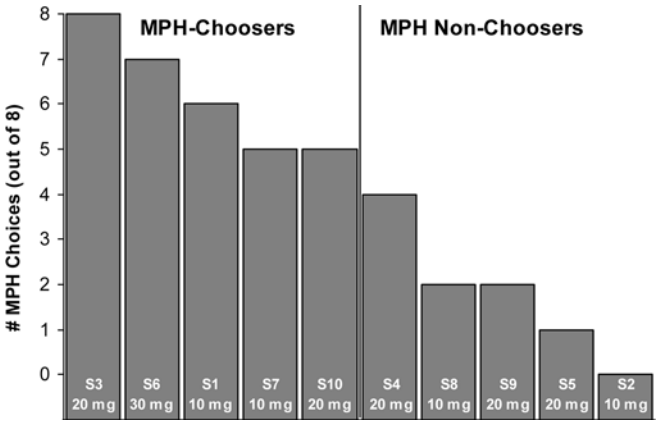

Fig. 2 Individual patterns of methylphenidate (MPH) preference for all subjects. MPH choosers were those selecting MPH five or more times (Chait 1994). *Figures* inside bars represent subject numbers and dose of MPH used to assess preference

effects during sampling sessions, while non-choosers did not report reliable changes across sampling sessions. Specifically, participants who experienced a significant reduction in ADHD symptoms during sampling sessions were more likely to select MPH during choice sessions. Moreover, MPH choosers reported significantly higher ratings of perceived effectiveness of their MPH than non-choosers prior to the study (mean for choosers=4.8/5.0, mean for non-choosers=3.2/5.0; t=1.9, P=0.04).

Discussion

The results demonstrate that, as a group, adults with ADHD chose to take MPH significantly more frequently than they chose to take either placebo or no capsules. Within the group, however, clear patterns of preference were evident. Half of the sample chose MPH more frequently than the other two options, and this pattern of preference was related to therapeutic efficacy as measured by reduction in ADHD symptoms following administration of the drug. The other half of participants who did not choose to take MPH exhibited lower levels of baseline ADHD symptoms and reported lower baseline efficacy of their prescribed dose.

Whereas drug reinforcement measured by choice procedures is often interpreted as being indicative of a drug's abuse potential (deWit and Johanson 1987), the present study lends support for the notion that, in clinical samples, drug preference may instead be associated with clinical efficacy. Examination of the patterns of drug preference alongside participant-rated effects shows clearly that MPH decreased ADHD symptoms without significant concomitant changes in either mood effects or stimulant-like effects. Moreover, clinically diagnosed individuals for whom ADHD symptoms were not impacted by MPH chose not to self-administer the drug reliably. These findings are comparable with those reported previously with anxious patients who reliably chose to self-administer alprazolam, but not in a manner indicative

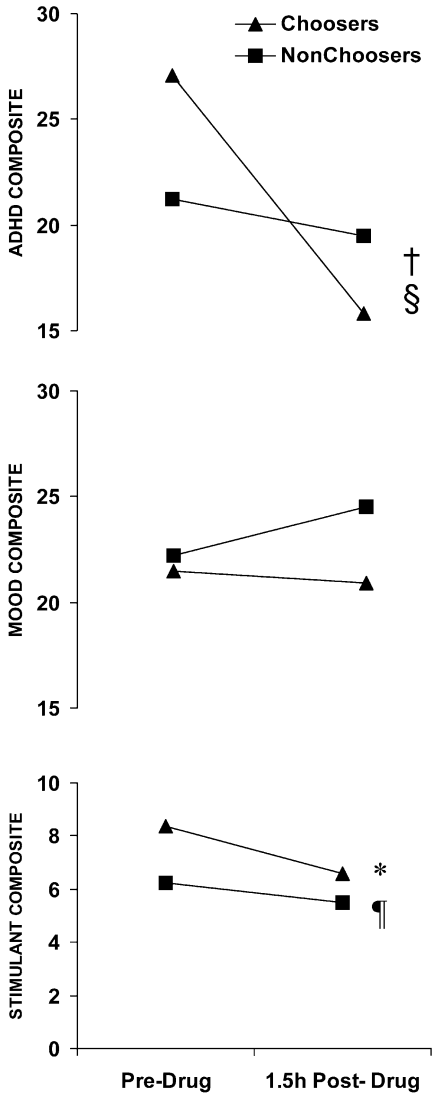

Fig. 3 Participant-rated effects for methylphenidate (MPH) choosers and non-choosers for the three rationally derived participant-rated effects composites. Data were drawn from sampling sessions and represent averages at pre-drug and 1.5 h after MPH administration. † Significant effect of time: $F_{1,8}$=16.7, P=0.03; § significant effect of time×group: $F_{1,8}$=9.0, P=0.01; * significant effect of group: $F_{1,8}$=5.7, P=0.04; ¶ significant effect of time: $F_{1,8}$=30.3, P=0.001

of abuse potential (Roache et al. 1997). Compared with other human studies of MPH preference, the results of this experiment may be most similar to Roehrs et al. (1999) in that the reinforcing effects of MPH may be context specific. As the reinforcing effects of MPH were associated with the contextual variable of sleep deprivation (Roehrs et al. 1999), the reinforcing effects of MPH in the present study may be associated with contextual variables of attentional disturbances (severity of ADHD symptoms). Indeed, results suggest that, during sampling sessions, MPH choosers exhibited a greater reduction in ADHD symptoms following MPH administration. Although during sampling sessions the non-choosers reported mild reduction in ADHD symptoms following

MPH, these changes were not significant. This suggests that the reinforcing effects of MPH are related to the clinical efficacy of MPH such that the more effective MPH was in reducing ADHD symptoms, the more likely it was chosen over placebo. Of note, the CAARS and WURS scores at screening did not differ between choosers and non-choosers, indicating that the groups were not different from a clinical standpoint, but rather in how their ADHD symptoms were impacted by MPH administration.

This study has several important implications. First, it adds to a sparse literature on the reinforcing effects of MPH in humans and is the first to study these effects in a sample of individuals receiving the drug for clinical purposes. Previous studies have reported discrepant results. One study failed to report consistent reinforcing effects (Chait 1994); one study reported reinforcing effects under specific conditions of sleep deprivation (Roehrs et al. 1999); and two studies reported significant reinforcing effects relative to placebo (Rush et al. 2001; Stoops et al. 2003).

Similar to the Roehrs et al. (1999) study wherein the reinforcing effects of MPH were associated with conditions of sleep deprivation, the reinforcing effects of MPH in the present study may be associated with conditions of distractibility, inattention or restlessness. For example, anecdotal subject comments suggest that participants chose MPH when they needed to study or had class. Moreover, participants reported not choosing MPH when they "wanted to take a nap" or "had nothing to do." Previous studies have demonstrated that the behavioral requirements following drug administration (i.e., vigilance or relaxation activities) can alter the self-administration of stimulants (i.e., caffeine and *d*-amphetamine) and sedatives (i.e., triazolam) (Silverman et al. 1994a,b). Based on these findings, the authors suggested that drug self-administration is related to the changes in environmental conditions. Thus, conditions of sleep deprivation, inattention and distractibility may function to increase the reinforcing efficacy of MPH. Unfortunately, in this study, the demands placed on participants following drug choice were not experimentally manipulated. Previous clinical research with children with ADHD has suggested that response to MPH and other stimulants is impacted by both child characteristics and the demands of the task evaluated (Rapport et al. 1985). Subsequent research would benefit from systematically addressing this issue and determining whether MPH preference in individuals with ADHD varies specifically as a function of subsequent behavioral requirements.

Continued research examining the conditions associated with MPH preference in clinical and non-clinical samples will also be important from the standpoint of assessing the abuse potential of MPH. The reinforcing effects of a substance are typically used to assess the abuse potential of that drug in human participants and it is widely accepted that drug reinforcement is closely associated with abuse liability (Fischman and Mello 1989). This study and others (Roache et al. 1997), however, emphasize the need to examine multiple endpoints (e.g., subjective effects and reinforcing effects) in order to differentiate abuse potential from therapeutic efficacy when psychoactive drugs are examined in clinical samples.

Indeed, the reinforcing effects of a clinically used agent may reflect therapeutic efficacy such that the choice of drug over placebo may be negatively reinforced by the consequences of eliminating aversive stimuli (e.g., anxiety; Roache et al. 1997) or may be positively reinforced with consequences such as being able to work more efficiently, receiving greater praise from teachers and peers, or getting better grades (as may be the case with ADHD). Assessing drug preference along with clinically relevant subjective effects as demonstrated in the present study is one way to determine correlates of drug preference and distinguish between abuse potential and therapeutic efficacy.

Compared with non-choosers, MPH choosers in this study reported more effectiveness of their medication outside the context of the study. Non-choosers typically reported relatively little benefit from their MPH dose and preferred placebo significantly more often than MPH. Yet, these individuals continue to take their prescribed medication despite the lack of clinical efficacy. This raises an important issue regarding the variables that are maintaining drug administration in these individuals. It may be the case that the combination of drug-preference procedures and assessment of clinically relevant subjective effects could be used in clinical contexts to titrate patients to optimal doses. Although MPH has been shown in controlled trials to have clear benefits for adults (Faraone et al. 2004), many primary caregivers are not familiar with titration and medication management in adults with ADHD. As such, procedures that can help these caregivers identify optimal dosing strategies are needed in the field.

Also of note in these experiments is the characteristic lack of subjective ratings of typical stimulant effects. A number of other studies have demonstrated that orally administered MPH as low as 20 mg results in significant changes in ratings of "high" and other effects associated with abuse potential (e.g., Heil et al. 2002; Kollins et al. 1998; Rush et al. 1998). Despite the reinforcing effects reported in the present study, we found much more variable stimulant-related subjective effects. Such results suggest further that MPH may exert a differential profile of abuse potential in individuals with ADHD compared with non-diagnosed individuals.

Research suggests that neuropharmacological differences may contribute to differential abuse potential in individuals diagnosed with ADHD relative to non-diagnosed individuals. Evidence supports the idea that neuropharmacological differences exist between diagnosed and non-diagnosed individuals with respect to dopamine functioning. Specifically, individuals diagnosed with ADHD differ from non-diagnosed controls with respect to dopamine transporter (DAT) density (Dougherty et al. 1999). These differences may contribute to the expression of ADHD symptoms and the efficacy of MPH treatment. Moreover, since individual differences in dopamine functioning may also influence the abuse

potential of MPH (Volkow et al. 1999, 2002), it stands to reason that those differences observed in patients with ADHD may be associated with a lower abuse potential of MPH than non-diagnosed controls. Studies that directly compare the abuse potential of MPH in groups of individuals with and without ADHD are needed to further explore this neuropharmacological hypothesis.

In general, the present experiment suggests that, although MPH does produce reinforcing effects in individuals with ADHD, these effects are more closely associated with clinical efficacy than with abuse potential of the drug. Subsequent research in this area should compare the abuse potential of MPH and other clinically used stimulants in samples of individuals with and without ADHD, as well as manipulating the behavioral demands following drug administration.

References

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn. Author: Washington, DC

Babcock Q, Bryne T (2000) Student perceptions of methylphenidate abuse at a Public Liberal Arts College. J Am Coll Health 49:143–146

Balster RL, Bigelow GE (2003) Guidelines and methodological reviews concerning drug abuse liability assessment. Drug Alcohol Depend 70:S13–S40

Barkley RA (1990) Attention-deficit hyperactivity disorder: a handbook for diagnosis and treatment. Guilford, New York

Biederman J, Faraone SV, Spencer T, Wilens T, Norman D, Lapey KA, Mick E, Lehman B, Doyle A (1993) Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. Am J Psychiatry 150:1792–1798

Chait LD (1994) Reinforcing and subjective effects of methylphenidate in humans. Behav Pharmacol 5:281–288

Chait LD, Uhlenhuth EH, Johanson CE (1987) Reinforcing and subjective effects of several anorectics in normal human volunteers. J Pharmacol Exp Ther 242:777–783

Conners CK, Erhardt D, Epstein JN, Parker JD, Sitarenios G, Sparrow E (1999a) Self-ratings of ADHD symptoms in adults. I. Factor structure and normative data. J Atten Disord 3:141–151

Conners CK, Erhardt D, Sparrow E (1999b) Conners's adult ADHD rating scales (CAARS). Multi-health systems. North Tonawanda, NY

Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ (1999) Dopamine transporter density in patients with attention deficit hyperactivity disorder [comment]. Lancet 354:2132–2133

Drug Enforcement Administration (2000): DEA congressional testimony by Terrance Woodworth before the Committee on Education and the Workforce: Subcommittee on Early Childhood, Youth and Families. World Wide Web url: http://www.usdoj.gov/dea/pubs/cngrtest/ct051600.htm. May 16, 2000

DuPaul GJ, Barkley RA, Connor DF (1998) Stimulants. In: Barkley RA (ed) Attention deficit hyperactivity disorder: a handbook for diagnosis and treatment, 2nd edn. Guilford, New York, pp 510–551

Faraone SV, Spencer T, Aleardi M, Pagano C, Biederman J (2004). Meta-analysis of the efficacy of methylphenidate for treating adult attention-deficit/hyperactivity disorder. J Clin Psychopharmacol 24:24–29

Fischman MW (1989) Relationship between self-reported drug effects and their reinforcing effects: studies with stimulant drugs. In: Fischman MW, Mello NK (eds) Testing for the abuse liability of drugs in humans. DHHS Publication No. (ADM) 89-1613. Nida Research Monograph 92, pp 211–230

Fischman MW, Mello NK (1989) Testing for abuse liability of drugs in humans. National Institute on Drug Abuse Monograph No. 92, Department of Health and Human Services Publication No. (ADM) 1989; 89-1613. US Government Printing Office, Washington, DC

Foltin RW, Fischman MW (1991) Methods for the assessment of abuse liability of psychomotor stimulants and anorectic agents in humans. Br J Addict 86:1633–1640

Fulton AI, Yates WR (1988) Family abuse of methylphenidate. Am Fam Physician 38:143–145

Gittelman R, Mannuzza S, Shenkar R, Bonagura N (1985) Hyperactive boys almost grown up. I. Psychiatric status. Arch Gen Psychiatry 42:937–947

Gomez TH, Roache JD, Meisch RA (2002) Orally delivered alprazolam, diazepam, and triazolam as reinforcers in rhesus monkeys. Psychopharmacology 161:86–94

Greenhill LL (1998) Childhood attention deficit hyperactivity disorder: pharmacological treatments. In: Nathan PE, Gorman JM (eds) A guide to treatments that work. Oxford University, New York, pp 42–64

Heil SH, Holmes HW, Bickel WK, Higgins ST, Badger GJ, Laws HF, Faries DE (2002) Comparison of the subjective, physiological, and psychomotor effects of atomoxetine and methylphenidate in light drug users. Drug Alcohol Depend 67:149–156

Heishman SJ, Henningfield JE (1991) Discriminative stimulus effects of *d*-amphetamine, methylphenidate and diazepam in humans. Psychopharmacology 103:436–442

Jaffe SL (1991) Intranasal abuse of prescribed methylphenidate by an alcohol and drug abusing adolescent with ADHD. J Am Acad Child Adolesc Psychiatry 30:773–775

Johanson CE, Uhlenhuth EH (1982) Drug preference in humans. Fed Proc 41:228–233

Johanson CE, deWit H (1989) The use of choice procedures for assessing the reinforcing properties of drugs in humans. In: Fischman MW, Mello NK (eds) Testing for abuse liability of drugs in humans. National Institute on Drug Abuse Research Monograph No. 92. US Government Printing Office, Washington, DC, pp 171–210

Johanson CE, Kilgore K, Uhlenhuth EH (1983) Assessment of dependence potential of drugs in humans using multiple indices. Psychopharmacology 81:144–149

Juergens S (1991) Alprazolam and diazepam: addiction potential. J Subst Abuse Treat 8:43–51

Kollins SH (2003) Comparing the abuse potential of methylphenidate versus other stimulants: a review of available evidence and relevance to the ADHD patient. J Clin Psychiatry 64[Suppl 11]:14–18

Kollins SH, Rush CR, Pazzaglia PJ, Ali JA (1998) Comparison of acute behavioral effects of sustained-release and immediate-release methylphenidate. Exp Clin Psychopharmacol 6:367–374

Kollins SH, MacDonald EK, Rush CR (2001) Assessing the abuse potential of methylphenidate in nonhuman and human subjects: a review. Pharmacol Biochem Beh 68:611–627

Lambert NM, Hartsough CS (1998) Prospective study of tobacco smoking and substance dependencies among samples of ADHD and non-ADHD participants. J Learn Disabil 31:533–544

Llana ME, Crismon ML (1999) Methylphenidate: increased abuse or appropriate use? J Am Pharmacol Assoc 39:526–530

Marsh LD, Key JD, Payne TP (2000) Methylphenidate misuse in substance abusing adolescents. J Child Adolesc Subst Abus 9:1–14

Martin WR, Sloan JW, Sapira JD, Jasiniski DR (1971) Physiologic, subjective and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine and methylphenidate in man. Clin Pharmacol Ther 12:245–258

McCann BS, Scheele L, Ward N, Roy-Byrne P (2000) Discriminant validity of the Wender Utah rating scale for attention-deficit/hyperactivity disorder in adults. J Neuropsychiatry Clin Neurosci 12:240–245

McCracken SG, deWit H, Uhlenhuth EH, Johanson CE (1990) Preference for diazepam in anxious adults. J Clin Psychopharmacol 10:190–196

McNair DM, Lorr M, Droppleman LF (1971) Profile of mood states (manual). Educational and Industrial Testing Services, San Diego

Musser CJ, Ahmann FW, Mundt P, Broste SK, Mueller-Rizner N (1998) Stimulant use and the potential for abuse in Wisconsin as reported by school administrators and longitudinally followed children. J Dev Behav Pediatr 19:187–192

Parran TV Jr, Jasinski DR (1991) Intravenous methylphenidate abuse. Prototype for prescription drug abuse. Arch Intern Med 151:781–783

Popper CW (1995) Combining methylphenidate and clonidine: pharmacologic questions and news reports about sudden death. J Child Adolesc Psychopharmacol 5:157–166

Rappley MD (1997) Safety issues in the use of methylphenidate. Drug Saf 17:143–148

Rapport MD, DuPaul GJ, Stoner G, Birmingham BK, Masse G (1985) Attention deficit disorder with hyperactivity: differential effects of methylphenidate on impulsivity. Pediatrics 76:938–943

Roache JD, Stanley MA, Creson DR, Shah NN, Meisch RA (1997) Alprazolam-reinforced medication use in outpatients with anxiety. Drug Alcohol Depend 45:143–155

Robinson LM, Sclar DA, Skaer TL, Galin RS (1999) National trends in the prevalence of attention-deficit/hyperactivity disorder and the prescribing of methylphenidate among school-age children: 1990–1995. Clin Pediatr 38:209–217

Roehrs T, Papineau K, Rosenthal L, Roth T (1999) Sleepiness and the reinforcing and subjective effects of methylphenidate. Exp Clin Psychopharmacol 7:145–150

Rush CR, Kollins SH, Pazzaglia PJ (1998) Discriminative-stimulus and participant-rated effects of methylphenidate, buproprion, and triazolam in *d*-amphetamine trained humans. Exp Clin Psychopharmacol 6:32–44

Rush CR, Essman WD, Simpson CA, Baker RW (2001) Reinforcing and subject-rated effects of methylphenidate and *d*-amphetamine in non-drug abusing humans. J Clin Psychopharmacol 21:273–286

Safer DJ (2000) Are stimulants overprescribed for youths with ADHD? Ann Clin Psychiatry 12:55–62

Safer DJ, Zito JM, Fine EM (1996) Increased methylphenidate usage for attention deficit disorder in the 1990s. Pediatrics 98:1084–1088

Silverman K, Kirby K, Griffiths RR (1994a) Modulation of drug reinforcement by behavioral requirements following drug ingestion. Psychopharmacology 114:243–247

Silverman K, Mumford GK, Griffiths RR (1994b) Enhancing caffeine reinforcement by behavioral requirements following drug ingestion. Psychopharmacology 114:424–432

Spencer TW et al (1995) A double-blind, crossover comparison of methylphenidate and placebo in adults with childhood-onset attention-deficit hyperactivity disorder. Arch Gen Psychiatry 52:434–443

Spiga R, Roache JD (1997) Human drug self-administration: a review and methodological critique. In: Johnson BA, Roache JD (eds) Drug addiction and its treatment: nexus of neuroscience. Lippincott-Raven Publishers, Philadelphia, pp 39–71

Stein MA, Sandoval R, Szumowski E, Roizen N, Reinecke MA, Blondis TA, Klein Z (1995) Psychometric characteristics of the Wender Utah rating scale (WURS): reliability and factor structure for men and women. Psychopharmacol Bull 31:425–433

Stoops WW, Glaser PEA, Rush CR (2003) Reinforcing, subject-rated, and physiological effects of intranasal methylphenidate in humans: a dose-response analysis. Drug Alcohol Depend 71:179–186

Volkow ND, Wang GJ, Fowler JS, Gatley SJ, Logan J, Ding YS, Dewey SL, Hitzemann R, Gifford AN, Pappas NR (1999) Blockade of striatal dopamine transporters by intravenous methylphenidate is not sufficient to induce self-reports of "high." J Pharm Exp Ther 288:14–20

Volkow ND, Wang GJ, Fowler JS, Thanos P, Logan J, Gatley SJ, Gifford A, Ding YS, Wong C, Pappas N (2002) Brain DA D2 receptors predict reinforcing effects of stimulants in humans: replication study. Synapse 46:79–82

Ward MF, Wender PH, Reimherr FW (1993) The Wender Utah rating scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. Am J Psychiatry 150:885–890

Wilens TE, Biederman J, Spencer TJ, Prince J (1995) Pharmacotherapy of adult attention deficit/hyperactivity disorder: a review. J Clin Psychopharmacol 15:270–279

Wilens TE, Faraone SV, Biederman J, Gunawardene S (2003) Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics 111:179–185

deWit H, Griffiths RR (1991) Testing the abuse liability of anxiolytics and hypnotic drugs in humans. Drug Alcohol Depend 28:83–111

deWit H, Johanson CE (1987) A drug preference procedure for use with human volunteers. In: Bozarth M (ed) Methods of assessing the reinforcing properties of abused drugs. Springer-Verlag, New York, pp 559–572

deWit H, Uhlenhuth EH, Johanson CE (1984) Lack of preference for flurazepam in normal volunteers. Pharmacol Biochem Behav 21:865–869

deWit H, Uhlenhuth EH, Hedeker D, McCracken SG, Johanson CE (1986) Lack of preference for diazepam in anxious volunteers. Arch Gen Psychiatry 43:533–541

Woods JH, Winger G (1995) Current benzodiazepine issues. Psychopharmacology 188:107–115

Zarin DA, Suarez AP, Pincus HA, Kupersanin BA, Zito JM (1998) Clinical and treatment characteristics of children with attention deficit hyperactivity disorder (ADHD) in psychiatric practice. J Am Acad Child Adolesc Psychiatry 37:1262–1270

Zito JM, Safer DJ, dosReis S, Gardner JF, Boles M, Lynch F (2000) Trends in the prescribing of psychotropic medications to preschoolers. JAMA 283:1025–1030