

A Pilot Study of Methylphenidate Preference Assessment in Children Diagnosed with Attention-Deficit/Hyperactivity Disorder

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ABSTRACT

Objective: The use of methylphenidate (MPH) in the treatment of attention-deficit/hyperactivity disorder (ADHD) is widely accepted; however, there is increased concern regarding its abuse potential. Few studies have examined the reinforcing effects of drugs in individuals receiving them for clinical purposes. This study attempts to assess MPH preference in children with ADHD using a choice procedure in order to explore the relationship among drug preference, clinical efficacy, and abuse potential.

Methods: Participants were 5 children (10–14 years of age) receiving MPH for the treatment of ADHD. Reinforcing effects were assessed using a double-blind choice procedure, with six sampling sessions and six choice sessions. Participant-rated effects were measured using self-report questionnaires. Clinical effects were measured using direct observations and behavior ratings.

Results: Differences between the number of MPH, Placebo, and Neither choices across participants were significant ($\chi^2 = 9.6$; $p < 0.01$). Three of five participants reliably chose MPH more often than placebo. MPH produced idiosyncratic patterns of participant-rated effects but failed to produce significant clinical effects.

Conclusions: These findings add to the literature on the reinforcing effects of MPH and are the first reported in a clinical sample of children. Further research exploring the role of clinical efficacy in MPH preference is warranted.

INTRODUCTION

ATENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is one of the most commonly diagnosed childhood psychiatric disorders in the United States, functionally impairing 3%–5% of the school-age population (APA 2000). ADHD is characterized by a persistent pattern of inattention and/or impulsivity-hyperactivity that is more frequent and severe than typically observed in individuals at comparable levels of development (APA 2000). To address these be-

havioral problems, most individuals diagnosed with ADHD receive pharmacological treatment, with the majority of prescribed products being methylphenidate-based (Robinson et al. 1999; Zarin et al. 1998; Zito et al., 2000).

Methylphenidate (MPH) has been shown to have positive effects across a wide range of domains (DuPaul et al. 1998; Greenhill 1998) including: Academic productivity and accuracy (DuPaul et al. 1994; Elia et al. 1993); fidgetiness and motor restlessness (DuPaul et al. 1994); parent and teacher behavior ratings (Barkley

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1991); aggression and other antisocial behavior (Bukstein and Kolko 1998), and social functioning and peer relations (Barkley 1989). Although MPH is associated with a wide range of clinically beneficial effects, the specific mechanisms by which the drug alters behavior have not been conclusively determined. From a neuropharmacological perspective, MPH is believed to exert its clinical effects through its action on noradrenergic and dopaminergic pathways (Solanto 2000). Specifically, the increase in intrasynaptic dopamine through a blockade of the dopamine transporter by MPH is hypothesized to attenuate deficits in inhibitory control and working memory that are hallmarks of ADHD (Greenhill et al. 1999). More recent work has proposed that MPH also serves to increase the salience of relevant environmental stimuli and that this may be another potential mechanism underlying clinical effects (Volkow et al. 2004).

Because MPH also exerts dopaminergic effects in the ventral tegmental area and nucleus accumbens through the mesolimbic pathway, it has been hypothesized to influence behavior by altering behavioral reinforcement processes (Johansen et al. 2002; Solanto 2000). Some support has been generated for this explanation of the behavioral mechanism of MPH. For example, one study demonstrated that MPH altered the rewarding properties of different kinds of stimuli in children with ADHD (Northup et al. 1997). Other studies have demonstrated that, compared to nondrug conditions, MPH changes the manner in which children with ADHD allocate their behavior across alternatives that produce rewards at different rates (Kollins et al. 1997; Murray and Kollins 2000).

In addition to altering reinforcement processes, MPH has been shown to function as a reinforcer itself through self-administration paradigms in nonhuman species (Aigner and Balster 1979; Johanson and Schuster 1975; Risner and Jones 1975). Traditionally, the reinforcing effects of a drug are considered to be one of the most powerful predictors of abuse because of the close correspondence between reinforcing effects and other measures of abuse potential (Balster and Bigelow 2003; Fischman 1989). However, only five 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 to placebo (8.6% of choices), and no capsules (63.8% of choices; Chait 1994); while the other study reported that 10 mg of 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).

To date, only one study has experimentally assessed the abuse potential of MPH in individuals with ADHD who are prescribed the drug for clinical purposes (Fredericks and Kollins 2004). In this study, MPH preference was assessed in a group of young adults diagnosed with ADHD using a double-blind choice procedure. Results indicated that, as a group, participants chose to take MPH significantly more frequently than they chose to take either placebo or no capsule. These results suggest that MPH produces reinforcing effects in individuals with ADHD, yet these effects were more closely associated with clinical efficacy than with abuse potential of the drug. Specifically, the participants who chose MPH reliably exhibited a greater reduction in ADHD symptoms following MPH administration and reported more effectiveness of their medication outside the context of the study. Thus, the reinforcing effects of MPH were seemingly associated with contextual variables of attentional disturbances such that the more effective MPH was in reducing ADHD symptoms, the more likely it was chosen over placebo.

This study is consistent with other research investigating the reinforcing effects of drugs in clinical samples to whom they are typically prescribed. For example, the reinforcing effects of diazepam and alprazolam—sedatives that have clearly demonstrated abuse potential in nonclinical samples (e.g., 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; de Wit 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. 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 et al. 2000 for a discussion) and that early stimulant treatment predisposes individuals with ADHD to develop problems with substance abuse (e.g., 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 only begun to be studied in patients for whom the medication is known to have clinical benefits (Fredericks and Kollins 2004). The reinforcing effects of MPH have not been assessed in children diagnosed with ADHD. Thus, the purpose of this study was to conduct a pilot investigation of MPH preference and participant-rated effects in children diagnosed with ADHD to further explore the distinction between a drug's therapeutic efficacy and its abuse potential.

METHODS

Participants

Participants for this study were 4 males (10–14 years of age) and 1 female (10 years of age), recruited through local physicians and psychologists, recruitment flyers, and word of mouth on the basis of two criteria: (1) an estab-

lished diagnosis of ADHD; and (2) a current prescription for MPH for the treatment of symptoms associated with ADHD. At the time of the study, all participants were receiving immediate-release MPH and had been receiving MPH treatment for at least 1 year prior to selection for the study. Parents provided informed consent, and participants provided verbal assent to participate.

To corroborate the ADHD diagnostic status of participants and to ensure a homogeneous group, the participants' parents, or one parent and another individual with whom the child had significant contact, completed the Child Behavior Checklist (CBCL; Achenbach and Edelbrock 1993; inclusion criterion = Attentional Problems subscales T score ≥ 65); and the Conners' Parent Rating Scale-48 (CPRS-48; Conners 1990; inclusion criterion = Impulsive-Hyperactive Scale T score ≥ 65). These instruments are used commonly in the assessment of ADHD, have adequate psychometric properties, and good predictive validity for identifying children with ADHD (e.g., Conners 1990; Hudziak et al. 2004). Parents were instructed to complete the rating forms based on their child's behavior when he or she was not on his or her medication. In addition, all participants had been previously diagnosed by pediatricians, family physicians, and/or other qualified clinicians and had been receiving MPH for at least 1 year. The primary care physicians for each participant also reviewed the protocol, approved participation and provided prescriptions for placebo pills and for the participant's normal dose of MPH. At the time of the study, all subjects were receiving immediate-release formulation MPH. Table 1 provides background information for each of the participants.

Participants were excluded from the study 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, and/or had a known family history of diabetes.* A total of 14 children were

*This exclusionary criterion was added at the request of the local IRB, as the placebo pills contained sugar. No participants were excluded for this reason.

TABLE 1. SUBJECT DEMOGRAPHICS

Subject	Age	Height	Weight	Time on MPH	Dose	CBCL ^a	CPRS-48 ^b	WISC-III ^c
1	10	4'11"	85 lbs	36 months	10 mg (t.i.d)	T = 69	T = 72	IQ = 91
2	14	5'7"	200 lbs	60 months	20 mg (b.i.d)	T = 81	T = 72	IQ = 68
3	10	NA	NA	36 months	10 mg (t.i.d)	T = 70	T = 76	IQ = 83
4	14	5'2"	100 lbs	84 months	30 mg (t.i.d)	T = 78	T = 76	IQ = 126
5 ^d	10	5'2"	100 lbs	12 months	10 mg (b.i.d)	T = 72	T = 87	IQ = 106

^aCBCL score represents the Attention Problems subtest score.

^bCPRS-48 score represents the Impulsive-Hyperactive subtest score.

^cWISC-III IQ score based on Block Design and Vocabulary scores.

^dSubjects 1–4 were male and subject 5 was female.

screened and 9 were excluded for the following reasons: receiving psychoactive medications in addition to MPH (4 children), not currently receiving MPH treatment (2 children), could not commit to the length of the study (2 children), did not meet age requirements (1 child).

Participants received monetary compensation for their participation in the 13 sessions. In addition, during experimental sessions, participants received assistance with outside homework assignments and practiced basic academic skills. The Human Subjects Institutional Review Board at Western Michigan University, Kalamazoo, MI, approved this work.

Procedure

Volunteers participated in 13 sessions. The first session was a screening session wherein the participant's parent completed the CBCL (Achenbach and Edelbrock 1993) and the CPRS-48 (Conners 1990). Parents were given an additional copy of these forms to be completed by another adult with whom the child had significant contact. Children were also administered a short form of the *Wechsler Intelligence Scale for Children*, 3rd edition (WISC-III, Block Design and Vocabulary subtests; Wechsler 1991) to screen for intellectual functioning. The scores obtained on the subtests of the WISC-III were not used as inclusion criteria. Rather, they were used to provide an estimate of the participant's ability to comprehend the questionnaires to be used in subsequent ses-

sions. In addition, medical history, comorbid mental health diagnoses, length of time on MPH, and dosing information were obtained. If inclusion criteria were met, the child's physician was contacted to provide a prescription for MPH and placebo capsules.

All drugs were prepared in a standardized manner by a pharmacist at the University Health Center who had experience preparing medications for other research and clinical activities in our laboratory. Each participant's maintenance dose of methylphenidate and an inert placebo were each prepared in opaque capsules (size 01). The participant's maintenance dose was encapsulated in one capsule, such that each participant received only one capsule at a time. Placebo and MPH capsules were placed in separate bottles labeled as "Bottle A" and "Bottle B." The capsule letter assignments were varied across participants. Participants were instructed that they would receive either their typical dose of MPH or placebo throughout the experiment but were informed that the same lettered capsule always contained the same substance.

Experimental sessions

For experimental sessions, participants were asked to refrain from taking their MPH prescription for at least 4 hours prior to coming into the laboratory. All participants were taking their maintenance dose of MPH at noon on experimental days. According to self-report,

participants were compliant with taking their noon dose 95% of the time. Participants 1, 2, and 4 each missed one of their noon doses, while participants 3 and 5 received their noon dose 100% of the time on experimental days. The 4-hour restriction on their medication administration did not deviate significantly from their typical medication regimen.

Sampling sessions. There were six sampling sessions, which occurred on Mondays and Tuesdays for 3 weeks. The sampling sessions were designed to provide participants experience with the effects of the two drug conditions (MPH and placebo) on the basis of which they would subsequently make their drug choice. During experimental sessions, participants arrived at the laboratory to complete participant-rated drug effect questionnaires (see Table 2 for timeline). Following the completion of the questionnaires, the participant took part in the appropriate drug administration procedures.

During the first sampling session of the week (on Monday), participants received either placebo or MPH in a capsule labeled "Pill A" or "Pill B." In the second sampling session (on Tuesday), participants received the other substance in a capsule labeled with the other letter. Participants also received a wristband 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. Participants were informed

that the same letter capsule would always contain the same thing (e.g., "real" medication or "pretend" medication). The order in which placebo and MPH were scheduled in the sampling sessions was counterbalanced across subjects and within-subjects across weeks. Drug administration was double-blind.

After drug-administration procedures, the participant was walked to an adjacent academic skills enrichment program. This setting included approximately 10 students (K-12), each of whom received individual instruction in basic skill areas, such as reading, math, writing, and spelling. Participants in this study were not formally enrolled in the tutorial program but still received individual instruction. They were seated at individual cubicles and had access to a desk and a computer wherein they worked on various academic tasks. While in this analog classroom setting, an independent observer began direct behavioral observations 45 minutes after the drug administration procedures and observed each subject for three 15-minute intervals using 30-second partial interval recording. During this time, the participant was directed to work on various math sheets and was observed for 15 minutes. Data were collected using the ADHD Behavior Coding System (Barkley 1990). Following the 15 minutes of independent seat work, the research participants and other students enrolled in the tutorial program took a break from academic work and were encouraged to participate in the break-time activities. During the break, the observer recorded behaviors using a Social Sit-

TABLE 2. AN EXAMPLE OF A SESSION TIMELINE INDICATING THE ORDER OF SESSION EVENTS

<i>Time</i>	<i>Activity</i>
1545 hour	Arrive at the laboratory and complete participant-rated effects questionnaires.
1600 hour	Drug administration procedures
1615 hour	Participants are escorted to the Project Help Facility
1645–1700 hour	Participants are given math sheets to complete during behavioral observations.
1700–1715 hour	Break time. Participants are observed during social interactions.
1720 hour	Participants return to the Project Help Facility and are given a second set of math sheets to complete during behavioral observations.
1735 hour	Research assistant completes the CTRS-28 form.
1745 hour	Participant returns to the lab to complete the participant-rated effects questionnaires.
1815 hour	Participant receives monetary compensation.

CTRS-28, Conners Teacher Rating Scale, 28-item version.

uations Behavioral Coding Form (adapted from Pelham et al. 1991). Following the break, participants returned to the classroom and were assigned a second set of math sheets and were observed for 15 minutes using the ADHD Behavior Coding System.

Two hours after the ingestion of the capsule the participant met with the researcher in the laboratory to complete the participant-rated effects questionnaires. After the completion of the questionnaires, the participant received monetary compensation from the researcher and was provided with verbal praise for their cooperation.

Choice sessions. There were six choice sessions, which occurred on Wednesdays and Thursdays for the same 3 weeks as the sampling sessions. In the choice sessions, participants were presented with three cups: One with "Pill A," one with "Pill B," and an empty cup labeled "C." The participant chose one of three options: To ingest "Pill A," to ingest "Pill B," or to take neither capsule. The use of a "Neither" option was included to replicate prior examinations 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). The number of times one substance was chosen over the other served as an indicator of its relative reinforcing effects (de Wit and Griffiths 1991). 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 (de Wit and Griffiths 1991; Foltin and Fischman 1991; Johanson and de Wit 1989). Following the choice, the child was presented with the appropriate letter-matched wristband, with "Neither" being labeled "C." The procedures for collecting participant-rated effects, and the behavioral observations in the academic skills enrichment program, 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 questionnaires. The participant-rated effects were assessed at pre-drug administration, and 1.5 hours postdrug administration. The participant-rated effects measures were as follows:

How I Feel Questionnaire. This is a 28-item questionnaire adapted from the van Kammen-Murphy Mood Scale (van Kammen and Murphy 1975). Items are rated on a 4-point scale (0 = Not at all; 1 = A little; 2 = Some; 3 = A lot). This adapted scale has been used with children to measure the subjective effects produced by caffeine (Elkins et al. 1981) and d-amphetamine (Rapoport et al. 1980).

Profile of Mood States (POMS). A short form of the POMS was used to assess mood and affective state. This version consists of 37 items that are rated on a 5-point scale (0 = Not at all; 1 = A little; 2 = Moderately; 3 = Quite a bit; 4 = Extremely). Compared to the original 65-item scale (McNair et al., 1971), the shortened version has been shown to have adequate psychometric properties (Shacham 1983). This scale has been used to assess the effects of stimulants in children (Walker et al. 1988). Six scales are derived from the 37 items: Anger/Hostility; Confusion/Bewilderment; Depression/Dejection; Fatigue/Inertia; Tension/Anxiety, and Vigor/Activity.

Subjective effects rating scale (SERS). This is a 22-item scale developed by Kollins et al. (1998) to assess the participant-rated effects of methylphenidate and other stimulant medication in children and adolescents. Items from the questionnaire are rated on a 4-point scale (0 = Not at all; 1 = A little; 2 = Some; 3 = A lot). Items on the SERS were derived from three sources. Firstly, stimulant-appropriate items from the Addiction Research Center Inventory (ARCI; Martin et al. 1971) were selected and changed to an age-appropriate reading level. Secondly, items were selected from the Side Effects Rating Scale (Barkley 1991). Lastly, items were selected based on discussions with clinicians experienced in working with children diagnosed with ADHD.

Visual Analog Scale (VAS). The VAS consisted of ten 100-mm horizontal lines, each labeled with a different item. Each scale was presented individually. Participants were instructed to rate each item on the basis of how they felt at the present time. Each VAS scale was anchored with "not at all" at the leftmost extreme, and "very much" at the rightmost extreme. Participants were instructed to place a mark on each line indicating how they felt at the moment. The items rated included Like Drug, Energetic, Sleepy, Friendly, Restless, Nervous, Hungry, Excited, Happy, and Feel Like Talking.

Clinical effects

ADHD behavior coding system. While participants completed their assigned math sheets, observers recorded the occurrences of off-task behavior, fidgetiness, vocalizing, playing with objects, and out of seat behavior using this coding system (Barkley 1990).

Social Situations Behavioral Coding Form. Observers recorded the occurrences of positive peer interactions, conduct problems, noncompliance, interrupting, and negative verbalizations using an adapted Social Situations Behavioral coding form (Pelham et al. 1991).

In order to collect reliability measurements on the ADHD and social behaviors, a second independent observer collected data during a minimum of 25% of the direct observations across participants. Interobserver agreement for all 10 categories was calculated separately by dividing the number of agreements by the number of agreements and disagreements and multiplying by 100. Interobserver reliability was at least 90% for each category for each of the 5 subjects.

Data analysis

Drug preference. The number of times MPH, Placebo, and Neither were chosen was taken as an indicator 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

the participants and examining the proportion of choices with a chi-square analysis.

Clinical effects. Behavioral observations and the number of math problems attempted and correctly completed were computed for MPH and placebo conditions and were analyzed using paired *t* tests.

Participant-rated effects. The participant-rated effects were analyzed for each participant. The change from baseline ((postdrug administration scores) – (predrug administration scores)) was computed for each questionnaire item or factor (e.g., POMS) using raw scores. Composite scores for each questionnaire were averaged for each participant at both time periods (pre, 1.5 hour). 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.

Change scores for each item or factor were computed for MPH sessions, Placebo sessions, and Neither sessions. The change scores for each condition (i.e., MPH, Placebo, Neither) were averaged for each participant. The average change scores for each item were then transformed into z-scores. The differences between z-scores obtained on MPH sampling days and Placebo sampling days were computed. In addition, differences between z-scores obtained on MPH, Placebo, and Neither choice days were computed. Lastly, differences between z-scores obtained on overall MPH and No Drug days (i.e., Placebo or Neither) were compared. Items that differed from the average by one standard deviation were considered to be meaningful changes.

RESULTS

Reinforcing effects

The results of the choice sessions were analyzed by examining the percentage of MPH choices per subject (see Fig. 1). Of 30 total choices across all participants (six choices each), MPH was chosen 18 times (60%). Placebo and neither were each chosen six times (20%). A chi-square analysis found that the number of

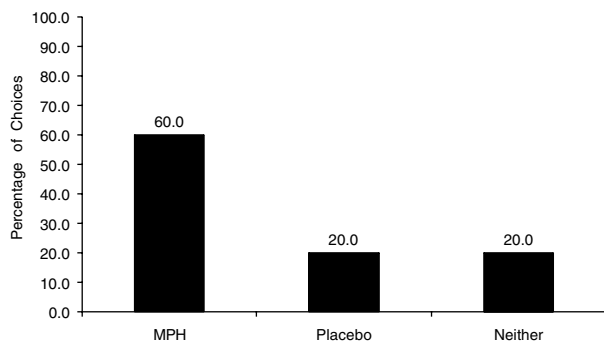


FIG. 1. The percentage of MPH, Placebo, and Neither choices across participants. MPH = methylphenidate.

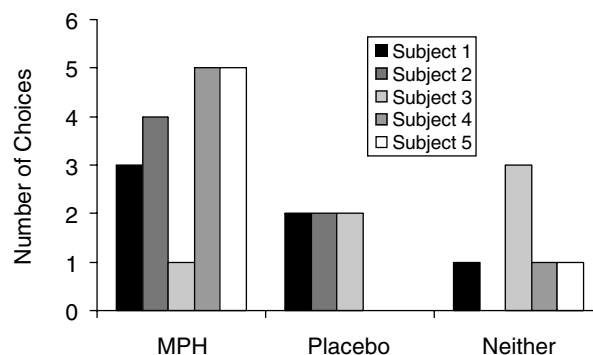


FIG. 2. The percentage of MPH, Placebo, and Neither choices for each participant. MPH = methylphenidate.

choices of MPH, Placebo, and Neither differed significantly ($\chi^2 = 9.6$; $p = 0.01$).

According to the criteria used by Chait (1994), participants 2, 4, and 5 were classified as "MPH choosers" (Fig. 2). Participant 2 chose MPH 4 of 6 times (67%) and placebo 2 of 6 times (33%). Participants 4 and 5 each chose MPH 5 of 6 times (83%) and Neither 1 time (16%). Participants 1 and 3 did not demonstrate reliable choice patterns and were classified as "nonchoosers," even though participant 1 chose MPH 3 of 6 times (50%) versus Placebo 2 of 6 times (33%) and Neither 1 of 6 times (16%). Participant 3 chose MPH 1 of 6 times (16%), Placebo 2 of 6 times (33%), and Neither 3 of 6 times (50%).

Clinical effects

Initial *t* tests on the categories used for behavioral observations and academic performance yielded no significant results. In addition, *t* tests on the measures of clinical effects revealed no significant differences between the sampling days and choice days. Thus, examining the interactions between the clinical effects, reinforcing effects, and subjective effects of MPH was not possible.

Participant-rated effects

Table 3 shows the results from the individual-subject analyses. The patterns of responding on the participant-rated effects questionnaires were idiosyncratic. For example, items typically associated with stimulant properties of

MPH, such as "Feel like Talking," "Energetic," and "Heart Beating Fast," did not yield consistent response patterns. Specifically, following MPH administration, some children reported an increase in these effects, others reported a decrease, and others reported no change. Likewise, responding on items typically associated with the clinical effects of MPH in ADHD populations was also variable. With 1 participant reporting an increase in "Can Concentrate," while 1 reported a decrease and the remaining 3 had no change. It is possible that with a larger sample, the participant-rated effects may have been more consistent.

DISCUSSION

The results of this pilot investigation demonstrated significant differences between the number of MPH, Placebo, and Neither choices in a sample of children diagnosed with ADHD. MPH was chosen more frequently than placebo or no capsules by 4 of 5 participants. In addition, MPH produced idiosyncratic patterns of subjective effects but failed to produce significant effects on behavior ratings or observations. These preliminary findings are concordant with research on the reinforcing effects of MPH in both nonhuman (Aigner and Balster 1979; Johanson and Schuster 1975; Risner and Jones 1975) and healthy adult human subjects (Roehrs et al. 1999; Rush et al. 2000). These findings are also consistent with another recently published study with college students with ADHD (Fredericks and Kollins 2004).

TABLE 3. PARTICIPANT-RATED EFFECTS FOR INDIVIDUAL SUBJECTS

<i>POMS subscales</i>	<i>Subject 1</i>	<i>Subject 2</i>	<i>Subject 3</i>	<i>Subject 4</i>	<i>Subject 5</i>
Tension	↓	—	↑	—	↓
Confusion	—	↑	—	—	—
Vigor	—	—	—	↓	—
<i>How I Feel Items</i>	<i>Subject 1</i>	<i>Subject 2</i>	<i>Subject 3</i>	<i>Subject 4</i>	<i>Subject 5</i>
Trouble keeping mind on things	↓	—	↓	—	—
Restless	↓	—	—	↓	—
"Funny"	↑	—	—	—	—
A lot of energy	↓	—	—	—	—
Tired and slow	↑	—	—	—	↓
Weird, "freaky"	—	—	—	—	—
No one wants to help me	—	↑	—	—	↓
Unusual thoughts	—	↑	—	—	—
Unhappy	—	—	↓	—	—
Doing a pretty good job	—	—	↑	—	↑
Something good will happen	—	—	—	↑	↑
Mad	—	—	—	—	↓
Friendly	—	—	—	—	↑
Happy	—	—	—	—	↑
<i>SERS</i>	<i>Subject 1</i>	<i>Subject 2</i>	<i>Subject 3</i>	<i>Subject 4</i>	<i>Subject 5</i>
Feel like talking	↓	—	—	—	↑
Can concentrate	↑	↓	—	—	—
Like joking	↓	↓	—	↑	—
Hungry	↓	—	—	—	—
Focused on work	—	↑	—	—	—
Popular	—	↓	↓	—	—
Get along with others	—	↓	—	—	—
Daydreamed	—	—	↓	—	—
Heart beating fast	—	—	↓	—	↑
Worked well	—	—	—	↑	—
Excited	—	—	—	↑	—
<i>Visual Analog Scales</i>	<i>Subject 1</i>	<i>Subject 2</i>	<i>Subject 3</i>	<i>Subject 4</i>	<i>Subject 5</i>
Energetic	↓	↓	—	—	—
Excited	—	↓	—	—	—
Like Drug	—	—	↑	↑	—
Sleepy	—	—	—	—	↓
Restless	—	—	—	—	↓

Note: Arrows indicate a significant deviation from the average change score across sessions. The direction of the arrows indicates the effect of MPH relative to the "no drug" condition (i.e., placebo or neither). Dashes indicate no significant differences.

POMS = Profile of Mood States; SERS = Subjective Effects Rating Scale.

This pilot study has several important implications. Firstly, 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 children receiving the drug for clinical purposes. To date, the literature is inconclusive with respect to whether methylphenidate exerts reinforcing effects in humans. 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 one study reported significant reinforcing effects compared to placebo using a progressive-ratio procedure (Rush et al. 2000). Our investigation is similar to the study that examined the reinforcing ef-

fects under conditions of sleep deprivation (Roehrs et al. 1999), in that the reinforcing effects of MPH may have been expressed only under a particular set of environmental conditions. For example, anecdotal subject comments suggested that children chose MPH when they "needed to calm down" or wanted "to be able to concentrate." This is also similar to the work completed by Silverman et al. (1994a, 1994b), which demonstrated that the behavioral requirements following drug administration (i.e., vigilance or relaxation activities) could alter the self-administration of stimulants (i.e., caffeine and d-amphetamine) and sedatives (i.e., triazolam). Based on these findings, the authors suggested that drug self-administration is related to the changes in environmental conditions.

Furthermore, this initial pilot study lends support to the idea that the reinforcing effects of a drug, as measured using choice procedures, are not necessarily associated with abuse potential, especially when assessed in clinical samples. The reinforcing effects of clinically used agents may necessitate a different conceptualization of such drug-taking behavior. In these situations, the choice of drug over placebo may be reinforced by the consequences of eliminating aversive stimuli (e.g., anxiety; Roache et al. 1997) or by more positive 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). This is also consistent with our previous study conducted with college students with ADHD (Fredericks and Kollins 2004). Future work that examines MPH in a context where there are measurable clinical changes will be important to help clarify the functional role of the reinforcing effects of the drug in this and other samples.

Despite the implications of this study, several important limitations should be addressed. Firstly, relevant clinical effects were not observed under MPH compared to placebo conditions. Although ADHD behaviors in analog classrooms and restricted academic situations are typically sensitive to the effects of stimulant medications (DuPaul et al. 1994; Swanson et al. 1998a; Swanson et al. 1998b), the setting used in our study may have precluded the observation of such clinical effects. In the Project

Help facility, participants in this study received one-on-one instruction in a cubicle with materials (computer games) and personnel (undergraduate tutors) that may have been more engaging for the participants than those materials and personnel typically used in a regular classroom or even an analog classroom setting. It would have been useful to collect concurrent data to corroborate the clinical effectiveness of the participant's medication in their regular classroom setting. Thus, it will be beneficial to replicate this study in a normal classroom setting (Abikoff and Gittelman 1985; Rapport et al. 1994), so as to gain a fuller understanding of the interaction between reinforcing and clinical drug effects in children with ADHD. It is also possible that the reinforcing effects of MPH that were observed reflected changes in motivation or alterations in the saliency of relevant environmental stimuli (e.g., Volkow et al. 2004) that our clinical battery was not able to assess. Future work would be well served to determine whether reliable MPH choice on clinical sample is associated with such endpoints.

A second limitation of our study surrounds the collection of participant-rated effects. Although the questionnaires used in this study have been used to measure subjective effects in children, the psychometric integrity of these instruments has not been determined in these populations. In addition, the reading level of the children may have affected the manner in which the subjective effects were evaluated, such that the participants may not have fully understood the items on the questionnaires. Thus, the lack of reading comprehension may have contributed to within-subject variability on the measures of subjective effects. The variable subjective effects reported by participants in this study may also reflect the possibility that stimulant drugs, such as MPH, produce different subjective effects among individuals diagnosed with ADHD as compared to nondiagnosed individuals. Indeed, among college students diagnosed with ADHD, MPH was associated with variable stimulant-rated subjective effects (Fredericks and Kollins 2004). Specifically, MPH decreased ADHD symptoms without significant changes in ratings of stimulant-like effects (e.g., "high"). This possibility is supported by studies reporting differ-

ential levels of dopamine transporter in the brains of ADHD individuals compared with non-ADHD controls, providing a possible neuropharmacological mechanism for the differential subjective effects (Krause et al. 2003).

Perhaps the biggest limitation of this study was our small sample size, which clearly limits the generalizability of the results. Previous studies examining the reinforcing effects of MPH in adults used larger sample sizes ($n = 35$, Chait 1994; $n = 6$, Roehrs et al. 1999; $n = 8$, Rush et al. 2000). Thus, in order to draw more confident conclusions about the reinforcing effects of MPH in children with ADHD, it will be important to replicate these findings with a larger subject population, while keeping in mind the practical and ethical challenges involved in doing this kind of work with clinical groups. One strategy for doing so might be to use less stringent entry criteria. Seven children were excluded from participating in the study because they were concomitantly receiving other medications, were not currently prescribed MPH, or did not meet minimum age criteria. Although the inclusion of heterogeneous participants with respect to these criteria would surely introduce additional variance to the obtained results, doing so might also help identify important individual differences in the reinforcing effects of MPH in a clinical sample.

CONCLUSIONS

In summary, the results of this pilot investigation suggest that MPH functions as a reinforcer in children for whom it is prescribed for the treatment of ADHD. These findings add to a growing literature on the reinforcing effects of this stimulant in humans and are the first to report such findings in a clinical sample of children. Because we did not observe reliable clinical effects of the drug, it is difficult to fully ascertain the implications of these findings in the context of clinical psychopharmacology. In any case, extension of the work begun here will be important to help understand the behavioral mechanism of action of MPH. Secondarily, further study of the reinforcing effects of MPH in individuals with ADHD may also shed light on the self-evaluations and attribu-

tional style of children diagnosed with ADHD and the abuse potential of MPH in individuals with ADHD.

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