

Comparison of the subjective, physiological, and psychomotor effects of atomoxetine and methylphenidate in light drug users

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Abstract

This study compared the subjective, physiological, and psychomotor effects of atomoxetine and methylphenidate with placebo in healthy volunteers. Sixteen non-dependent light drug users participated in six experimental sessions, receiving placebo, atomoxetine (20, 45 and 90 mg) and methylphenidate (20 and 40 mg) using a double-blind, Latin square design. Subjective drug effects were assessed using Visual Analog Scales (VAS), the Addiction Research Center Inventory (ARCI) and Adjective Rating Scales (ARS). Psychomotor performance was evaluated using the Digit Symbol Substitution Test (DSST). Physiological measures were also collected throughout the sessions. Assessments were conducted before drug administration and 30, 60, 90, 120, 150, 180 and 240 min following dosing. Forty milligrams methylphenidate produced significant increases on the stimulant portions of the VAS and ARS and the benzedrine, amphetamine, morphine-benzedrine and lysergic acid diethylamine (LSD) subscales of the ARCI relative to placebo. Ninety mg atomoxetine was reported to be unpleasurable relative to placebo as indicated by significant increases on the 'bad' and 'sick' portions of the VAS, and on the LSD subscale of the ARCI. Compared with placebo, both methylphenidate doses significantly increased systolic blood pressure (BP) and heart rate (HR). For atomoxetine, 90 mg increased diastolic BP, 45 and 90 mg increased systolic BP, and all three doses increased HR relative to placebo. Neither compound produced significant differences from placebo on DSST performance. These results suggest that atomoxetine does not induce subjective effects similar to methylphenidate and suggest that it is unlikely that atomoxetine will have abuse liability. © 2002 Published by Elsevier Science Ireland Ltd.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common disorder of childhood that affects 3–7% of school age children (DSM-IV-TR; American Psychiatric Association, 2000). It is associated with impairment of academic and social functioning (Hechtman, 2000), and a growing body of data suggests that it also is associated with considerable morbidity and poorer outcomes later

in life (Brown and Borden, 1986; Hechtman, 1996; Klein and Mannuzza, 1989, 1991; Thorley, 1984; Weiss, 1996; Weiss and Hechtman, 1993). Recent studies have demonstrated that drug therapy is associated with superior symptom reduction for most children compared with psychosocial interventions (MTA Cooperative Group, 1999).

Stimulants such as methylphenidate are currently the standard drug therapies for the treatment of pediatric and adult ADHD. While efficacious, methylphenidate has been classified as a Schedule II drug under the US Controlled Substances Act (Parran and Jasinski, 1991). In a recent review of the literature on the abuse potential of methylphenidate in non-human and human subjects, more than three-quarters of the studies reviewed re-

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ported that methylphenidate functioned behaviorally in a manner similar to d-amphetamine or cocaine, producing comparable reinforcing, discriminative-stimulus and/or subjective effects (Kollins et al., 2001). While rates of methylphenidate misuse/abuse have not been empirically established (Kollins et al., 2001), the similarity of methylphenidate's behavioral pharmacological profile to other abused stimulants suggests potential for abuse that has been a concern of regulatory agencies in many countries and of patients, parents, prescribers and school authorities. As a result, there has been considerable interest in developing a non-stimulant alternative for ADHD.

Although not yet approved for the treatment of ADHD, the efficacy of atomoxetine¹ has been evaluated in experimental studies of children and adults with ADHD (Michelson et al., 2001; Spencer et al., 1998, 2001). Reports from these studies suggest that atomoxetine is superior to placebo in reducing symptoms of ADHD, as evidenced by a 10–20% reduction in scores on the ADHD Rating Scale-IV in children, depending on dose and design (Michelson et al., 2001; Spencer et al., 2001), and a 28% reduction in adults (Spencer et al., 1998). These results suggest that atomoxetine is a promising candidate for further development as a treatment for ADHD.

Given the abuse potential of the current standard drug therapies for ADHD, it is important to assess the abuse liability of promising new drug therapies. The receptor binding profile of atomoxetine does not suggest the likelihood of abuse potential, with high selectivity for the norepinephrine transporter for both atomoxetine and the active metabolite 4-hydroxyatomoxetine (F.P. Bymaster, personal communication). Unlike psychostimulants, atomoxetine does not increase dopamine concentrations in the nucleus accumbens or other sites associated with abuse potential in animals (Bymaster et al., *in press*). Results of drug discrimination studies in animals have reported mixed results in assessing the generalization of atomoxetine to cocaine and methamphetamine, with some suggesting generalization (Terry et al., 1995; Johanson and Barrett, 1993; Sasaki et al., 1995; Spealman, 1995), and others reporting no significant generalization (Kleven et al., 1990; Tidey and Bergman, 1998). To our knowledge, there are no drug discrimination studies assessing generalization of atomoxetine in humans or self-administration studies of atomoxetine in either animals or humans. The present study sought to compare the subjective, physiological and psychomotor effects of atomoxetine and methyl-

phenidate, the positive control, to placebo in healthy volunteers with light drug use histories.

2. Methods

2.1. Study participants

Participants were 16 healthy adults (12 females and four males) whose average age was 20 years (range, 18–36). All participants were light drug users, with no history of drug or alcohol dependence other than nicotine. All participants reported a history of alcohol and marijuana use. Five participants had prior exposure to amphetamines and methylphenidate, but no participant reported more than ten uses in their life. Five participants reported experimentation with cocaine, but no more than 20 uses in their life. Four participants reported regular cigarette smoking, averaging 13 cigarettes per day (range, 5–30).

Participants were recruited via newspaper ads and fliers posted on bulletin boards. Prior to participation, they were screened to rule out major psychiatric and medical illnesses. Participants who were currently being treated for or had a history of treatment of ADD or ADHD were excluded from participation. Each received a full medical evaluation including an EKG.

The study was approved by the Committees on Human Research at the University of Vermont and was conducted in accordance with the Declaration of Helsinki 1975, as revised in 1983. Volunteers gave written informed consent prior to any study procedure or study drug administration and were paid for their participation. Participants were informed that the purpose of the study was to determine the effects of atomoxetine on psychological and physiological variables and that in addition to atomoxetine, they may receive an active comparator (methylphenidate) and/or an inactive study drug (placebo).

2.2. Drugs

Each participant was exposed to the following six drug conditions using a Latin square design: 20, 45 and 90 mg atomoxetine, 20 and 40 mg methylphenidate and placebo. All drugs were provided by Eli Lilly and Company (Indianapolis, IN) in identical capsule form. Two participants discontinued the study before receiving all six drug conditions, one due to scheduling conflicts and the other due to her doctor's wishes. The former received 20 mg methylphenidate and 45 mg atomoxetine prior to discontinuation, while the latter received 20 mg methylphenidate, 90 mg atomoxetine and placebo prior to discontinuation. Data from these sessions were included in the overall analyses. Study sessions were conducted in a double blind fashion, with

¹ Atomoxetine was originally called tomoxetine. The name was recently changed in order to avoid any potential confusion with tamoxifen that might lead to errors in dispensing.

the nurse, research assistant and participants blind to the study conditions.

2.3. Study sessions

Study sessions were separated by a minimum of 48 h. Participants were instructed to abstain from alcohol for 24 h and from caffeine, other liquids and solid food for 4 h prior to each study session. Participants were also instructed to abstain from all illicit drugs during the study and provided a urine sample prior to each session that was screened for opioids, cocaine, amphetamine, cannabinoids, methadone and benzodiazepines using the EMIT system (Syva Corp., San Jose, CA) to ensure compliance with study instructions. No drug positive urine samples were submitted during the study. Breathalyzer (0.00 required) and field sobriety tests (touching the nose with each hand with eyes closed; counting backwards from 100 by increments of seven; standing on one foot with eyes closed for 30 s; walking seven steps, heel to toe, backwards and forwards) were administered prior to each study session. Cigarette smoking was not permitted during study sessions.

The sessions were conducted in a quiet, temperature-controlled laboratory. Participants were required to remain semi-supine for the duration of each study session. Dependent measures were collected before drug administration and 30, 60, 90, 120, 150, 180 and 240 min following dosing. Participants were allowed to engage in sedentary activities in the laboratory, such as reading, when assessments were not scheduled. All participants were required to pass a field sobriety test prior to discharge from the laboratory.

Participants completed computer-based assessments of abuse potential and psychomotor performance measures on Macintosh iBook laptop computers (Apple, Cupertino, CA). Participants were seated in front of the computer with an attached keyboard with numeric keypad. The self-report questions and psychomotor task were presented on the computer screen and participant responses were recorded by the computer. This system has been found to be reliable and accurate in other laboratory studies (McLeod et al., 1982; Bickel et al., 1988).

2.4. Dependent measures

2.4.1. Subjective measures

The subjective effects of atomoxetine and methylphenidate were compared with placebo on several self-report questionnaires: Visual Analog Scales (VAS), Addiction Research Center Inventory (ARCI) short form and Adjective Rating Scales (ARS). On the VAS (Griffiths et al., 1984; Preston et al., 1988; Roache and Griffiths, 1989), participants rated the extent to which they experienced seven effects: 'bad', 'like', 'sick', 'good',

'sedated', 'stimulated' and 'would you take again'. The analog scales consisted of 100 mm lines, anchored at each end by 'not at all' and 'severe'. Participants were instructed to move a cursor along the line reflecting the degree to which they experienced each of the effects. Responses were recorded as a score ranging from 0 to 100.

Participants completed the ARCI short form, a 49-item true/false questionnaire that was derived from a longer 500-item questionnaire containing empirically-derived drug sensitive scales (Haertzen, 1970; Martin et al., 1971). The five major subscales of this questionnaire are: amphetamine (A; amphetamine-sensitive stimulation scale), benzedrine (BG; stimulant scale), lysergic acid diethylamide (LSD; a measure of dysphoria and psychomimetic effects), morphine-benzedrine (MBG; a measure of euphoria) and pentobarbital, chlorpromazine, alcohol (PCAG; a measure of sedation).

Self-reports of drug effects were rated on a modified version of the ARS, a 32-item questionnaire describing typical sedative and stimulant drug effects (Oliveto et al., 1993). For each adjective, participants were instructed to choose a button, ranging from 0 to 9, indicating the extent to which they experienced each effect. Stimulant and sedative scores were derived by summing the responses on the two sets of questions. Stimulant adjectives included items such as 'energetic' and 'good mood', and sedative adjectives included such items as 'relaxed' and 'lazy'.

2.4.2. Psychomotor task

Psychomotor performance was assessed using a computerized version of the Digit Symbol Substitution Test (DSST; McLeod et al., 1982). Briefly, one of nine possible patterns appeared for the participant to copy. The pattern was a 3 × 3 grid of squares that mirrors the layout of a 9-number keypad. Three of the squares were filled in on each model pattern and the participant had to duplicate that pattern on the 9-number keypad. Participants had 90 s to reproduce as many patterns as possible. The dependent measures were the number of patterns attempted and the number and percent of patterns correctly duplicated.

2.4.3. Physiological measures

Blood pressure (BP) and heart rate (HR) were monitored at each assessment point. Systolic and diastolic BP (mmHg) were determined oscillometrically by a Sentry II BP monitor (NBS Medical, Costa Mesa, CA) with an automatically inflating cuff. Heart rate (beats per minute) was also determined by the Sentry II monitor.

Table 1
Mean effects values for subjective and physiological outcome measures

Outcome measure	Placebo	MPH 20 mg	MPH 40 mg	MPH Trend	ATMX 20 mg	ATMX 45 mg	ATMX 90mg	ATMX trend
<i>VAS</i>								
Liking	40.43	40.85	43.55	NS	35.94	39.18	35.42	NS
Good	44.57	47.79	50.82	NS	42.92	44.92	39.61	NS
Bad	8.90	9.12	8.86	NS	7.95	12.36	16.81*	**
Sick	5.26	8.53	12.81	NS	7.85	13.96	16.23*	**
Stimulated	19.27	22.31	35.08*	**	19.95	17.53	22.17	NS
Sedated	13.44	14.31	12.45	NS	9.68	13.75	18.63	**
Take again	41.25	44.92	43.66	NS	38.28	41.25	32.76	NS
<i>ARCI</i>								
PCAG	14.85	14.42	15.54	NS	14.65	17.31	19.21	NS
BG	5.64	6.02	6.30	NS	5.65	5.81	5.36	NS
A	2.47	3.12	3.33	NS	2.29	2.48	2.17	NS
MBG	2.80	3.43	3.70	NS	2.63	2.81	1.90	NS
LSD	3.11	3.48	3.99*	NS	3.16	3.71	3.82	**
<i>ARS</i>								
Stimulated	21.87	23.78	27.22*	**	20.49	23.29	22.00	NS
Sedated	14.85	14.42	15.54	NS	14.65	17.31	19.21	NS
<i>Physiological measures</i>								
Diastolic BP	68.43	69.27	71.92	NS	69.11	71.45	72.86*	**
Systolic BP	113.23	120.54*	122.59*	NS	115.65	120.77*	124.00*	**
HR	67.42	75.23*	78.29*	NS	73.13*	75.76*	78.47*	**

MPH, methylphenidate; ATMX, atomoxetine; VAS, visual analog scale; ARCI, Addiction Research Center Inventory short form; PCAG, pentobarbital, chlorpromazine, alcohol; BG, benzedrine; A, amphetamine; MBG, morphine-benzedrine; LSD, lysergic acid diethylamide; ARS, Adjective Rating Scale; BP, blood pressure; HR, heart rate. *, Different from placebo at $P < 0.05$ (Dunnett's procedure); **, linear trend significant among active doses ($P < 0.05$); NS, linear trend not significant among active doses.

2.5. Data analysis

Analyses of variance corresponding to a replicated Latin square design were used to evaluate differences across treatment conditions (Montgomery, 1991). Since these analyses were based on all participants randomized, which included participants from an incomplete Latin square and participants not exposed to all treatment conditions, least square means were utilized for all statistical comparisons. Primary outcome measures were defined as average and peak effects over the 4 h following administration of active drug or placebo. No significant differences were observed across treatment conditions during the pretreatment period. Dunnett's procedure was used to compare means corresponding to active doses of atomoxetine and methylphenidate to placebo. Linear contrasts were constructed representing the linear dose effect within each drug to examine increasing or decreasing trends across the active doses. All statistical analyses were performed using SAS, PROC MIXED. Statistical significance was determined using $\alpha = 0.05$.

3. Results

3.1. Mean effects

3.1.1. Subjective measures

Table 1 presents a summary of the mean effect for all of the outcome measures at each of the six drug conditions. At each dose, those indices that showed significant differences from placebo are indicated by an asterisk. The high dose of atomoxetine (90 mg) was significantly different from placebo on the 'bad' and 'sick' portions of the VAS. Fig. 1(A and B) shows the time course for placebo, the two doses of methylphenidate and the three doses of atomoxetine for these two measures. There were also significant increasing linear trends across all atomoxetine doses for both of these measures as well as on the 'sedated' portion of the VAS and the ARCI LSD subscale.

In contrast, the high dose of methylphenidate (40 mg) significantly increased stimulant scores on both the VAS and the ARS. Fig. 1(C and D) shows the time course for the six drug conditions for these two measures. There

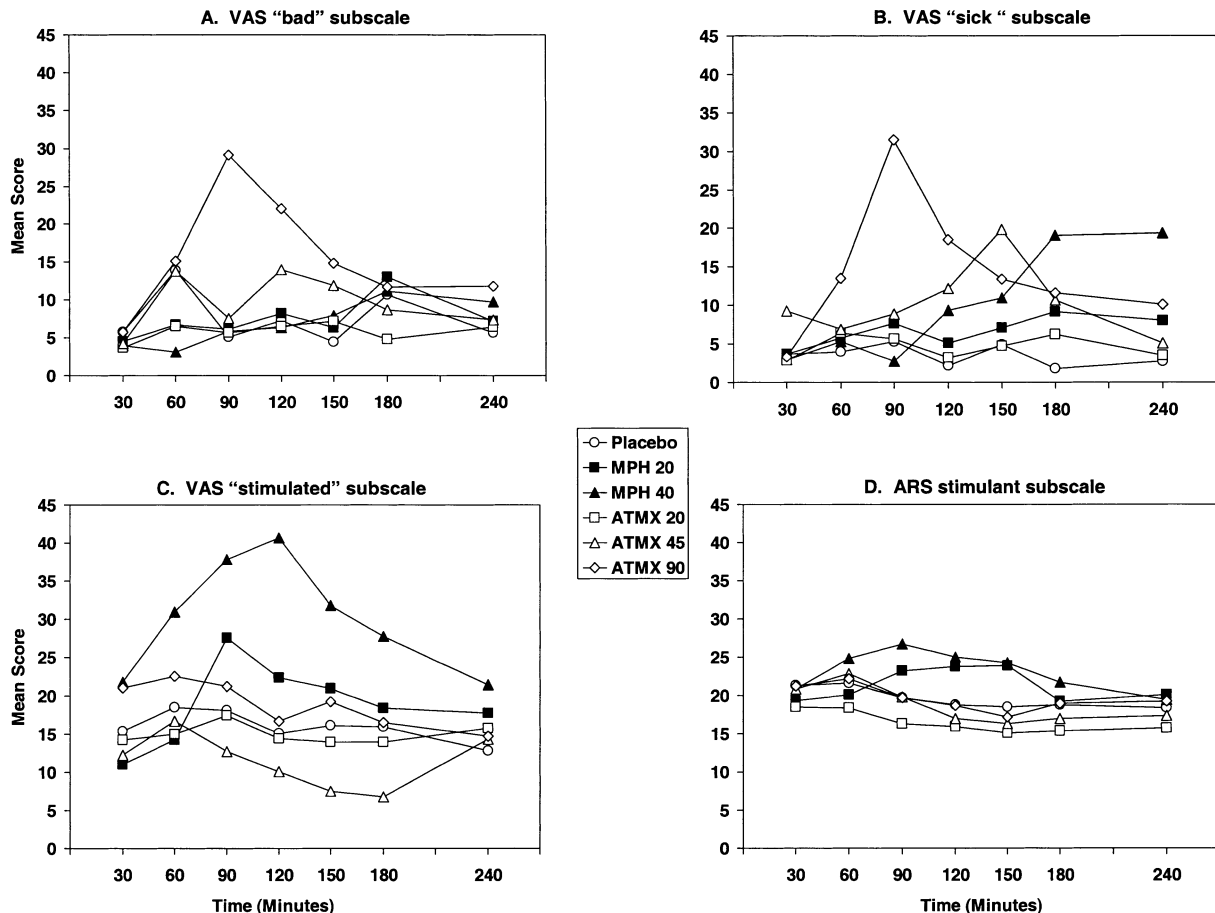


Fig. 1. Time effects on selected subjective outcome measures. Mean score for VAS 'bad' (A), VAS 'sick' (B), VAS 'stimulated' (C), and Adjective Rating Scale stimulant (D) subscales for each group over the course of the 4-h study period are presented. MPH, methylphenidate; ATMX, atomoxetine.

were also significant increasing linear trends across methylphenidate doses for both of these measures. Forty milligrams methylphenidate was also significantly different from placebo on the LSD scale of the ARCI.

3.2. Psychomotor task

Neither atomoxetine nor methylphenidate produced any significantly different changes from placebo or significant linear trends on any of the DSST measures analyzed (data not shown).

3.3. Physiological measures

Table 1 presents a summary of the mean effect for the physiological measures at each of the six drug conditions. Ninety milligram atomoxetine produced significant increases in diastolic BP compared with placebo and there was a significant increasing linear trend across atomoxetine doses. Both 45 and 90 mg atomoxetine produced significant increases in systolic BP, as well as a significant increasing linear trend across atomoxetine doses. Finally, all three doses of atomoxetine produced

significant increases in HR, as well as a significant increasing trend across atomoxetine doses.

Both doses of methylphenidate produced significant increases in systolic, but not diastolic BP. Both doses of methylphenidate also produced significant increases in HR. However, there was no significant linear trend across methylphenidate doses.

3.4. Peak effects

3.4.1. Subjective measures

Table 2 presents a summary of the peak effect for all of the outcome measures at each of the six drug conditions with significant differences from placebo again indicated by an asterisk. In agreement with mean effects, the peak effect of 90 mg atomoxetine was significantly different from placebo on the 'bad' and 'sick' portions of the VAS. In addition, 90 mg atomoxetine was significantly different from placebo on the ARCI LSD subscale. There were also significant increasing linear trends across atomoxetine doses for these three measures, as well as on the ARCI PCAG and on the sedation portions of both the VAS and the ARS.

Table 2
Peak effects values for subjective and physiological outcome measure

Outcome measure	Placebo	MPH 20 mg	MPH 40 mg	MPH trend	ATMX 20 mg	ATMX 45 mg	ATMX 90 mg	ATMX trend
<i>VAS</i>								
Liking	51.47	54.09	59.28	NS	47.72	50.73	52.78	NS
Good	52.30	60.41	64.19*	NS	52.18	59.46	57.38	NS
Bad	18.45	22.86	20.23	NS	12.97	36.32	38.74*	**
Sick	12.38	20.99	30.57	NS	15.64	30.76	35.91*	**
Stimulated	31.56	34.39	55.61*	**	24.18	27.77	35.05	NS
Sedated	24.63	30.45	27.40	NS	18.15	26.73	37.83	**
Take again	48.76	55.43	58.61	NS	46.22	53.71	49.86	NS
<i>ARCI</i>								
PCAG	20.85	23.34	25.24	NS	21.87	26.41	30.51	**
BG	6.57	6.97	7.55*	NS	6.40	6.46	6.33	NS
A	3.34	4.16	5.15*	NS	3.15	3.43	3.40	NS
MBG	3.78	5.05	6.23*	NS	3.75	4.37	2.92	NS
LSD	3.81	4.35	5.44*	**	3.76	4.41	5.69*	**
<i>ARS</i>								
Stimulated	27.52	32.00	37.09*	**	26.32	30.44	29.27	NS
Sedated	20.85	23.34	25.24	NS	21.87	26.41	30.51	**
<i>Physiological measures</i>								
Diastolic BP	78.46	78.21	79.22	NS	77.27	80.99	81.02	NS
Systolic BP	126.05	131.08	131.61	NS	126.60	131.61	135.02*	**
HR	75.04	83.30*	85.90*	NS	81.20	84.04*	91.16*	**

See Table 1 for abbreviations. *, Different from placebo at $P < 0.05$ (Dunnett's procedure); **, linear trend significant among active doses ($P < 0.05$); NS, linear trend not significant among active doses.

As with the mean effects, 40 mg methylphenidate was significantly different from placebo on the stimulant portions of the VAS and the ARS. In addition, the peak effect of 40 mg methylphenidate was significantly different from placebo for the VAS 'good' scale and for the BG, A, MBG and LSD subscales of the ARCI. Consistent with findings from mean effects, significant increasing linear trends across methylphenidate doses were apparent on the stimulated scales of both the VAS and the ARS, in addition to the LSD scale of the ARCI.

3.5. Psychomotor task

Neither atomoxetine nor methylphenidate produced any significantly different changes from placebo or significant linear trends on any of the DSST measures analyzed (data not shown).

3.5.1. Physiological measures

Table 2 presents a summary of the peak effect for the physiological measures at each of the six drug conditions. Ninety milligrams atomoxetine produced a significant increase in systolic BP compared with placebo and there was a significant increasing linear trend across atomoxetine doses. Both 45 and 90 mg atomoxetine produced significant increase in HR, as well as a significant increasing linear trend across atomoxetine doses.

Both doses of methylphenidate produced significant increases in HR compared with placebo, although there was no significant linear trend across methylphenidate doses.

4. Discussion

The results of this study indicate that, across the doses tested, participants receiving atomoxetine reported relatively few subjective drug effects different from placebo. Specifically, the highest atomoxetine dose produced increases in 'bad' and 'sick' scores of the VAS and linear trends across atomoxetine doses towards increased sedation on the VAS and ARS. Atomoxetine did not significantly affect scores on any of the ARCI scales, except for a peak effect for 90 mg atomoxetine on the LSD subscale and linear trends across atomoxetine doses for the PCAG and LSD subscales. Across the doses and time frame examined and with the instruments tested, atomoxetine does not engender pleasurable subjective drug effects, suggesting that it is unlikely that atomoxetine will have abuse liability.

In contrast, methylphenidate produced increases in many self-report measures sensitive to stimulant effects, including the stimulant scales of both the ARS and the VAS and the BG, A and MBG scales of the ARCI. These data add additional evidence to a number of

reports of significant increases on these measures after methylphenidate administration compared with baseline or placebo conditions (Chait, 1994; Heishman and Henningfield, 1991; Martin et al., 1971; Roehrs et al., 1999; Rush et al., 1998). Further, this constellation of effects associated with methylphenidate appears consistent across sample populations, including healthy adults and substance abusers, and a range of doses and routes of administration (Kollins et al., 2001).

While atomoxetine generally produced subjective drug effects that were in the opposite direction from methylphenidate, both the high doses of atomoxetine and methylphenidate produced small but significant increases on the ARCI LSD subscale. A number of items on this subscale describe dysphoric feelings, such as 'I have a disturbance in my stomach' and 'I feel drowsy', which parallel the sick and sedated feelings registered by the VAS and the ARS for atomoxetine. In contrast, there are items on this subscale that also contribute to scores on the A and BG stimulant-sensitive subscales of the ARCI, such as 'Some parts of my body are tingling' and 'I have a weird feeling'. These items may explain why two drugs with different subjective profiles produced similar effects on this subscale.

While neither compound affected psychomotor task performance, both atomoxetine and methylphenidate significantly affected physiological parameters. Atomoxetine produced dose-dependent increases in systolic BP and HR, while both doses of methylphenidate produced similar increases over placebo.

The findings of the current study must be considered in light of some methodological limitations, including the drug doses and the population tested. In the present study, each of the three doses of atomoxetine was delivered in one administration. Previous reports of treatment of children and adults with ADHD with atomoxetine typically spread the daily dose over two administrations (Michelson et al., 2001; Spencer et al., 1998, 2001). It remains unclear whether repeated administration of a moderate dose of atomoxetine would produce the same subjective profile as a single administration. The abuse liability of atomoxetine may also be different in populations other than the one tested in the present study. Future studies that systematically measure the subjective effects of atomoxetine in children and adults diagnosed with ADHD would be useful additions to the literature.

Despite these limitations, the present study begins to fill an important gap in the literature by allowing the comparison of findings from preclinical studies to human populations. The results suggest that atomoxetine, relative to placebo, does not produce subjective effects similar to methylphenidate in healthy volunteers with light drug use histories and that it is not likely to have abuse liability, making it a promising candidate for further development as a treatment for ADHD.

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