Effects of Low to Moderate Acute Doses of Pramipexole on Impulsivity and Cognition in Healthy Volunteers

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Abstract: The neurotransmitter dopamine is integrally involved in the rewarding effects of drugs, and it has also been thought to mediate impulsive behaviors in animal models. Most of the studies of drug effects on impulsive behaviors in humans have involved drugs with complex actions on different transmitter systems and different receptor subtypes. The present study was designed to characterize the effect of single doses of pramipexole, a D2/D3 agonist, on measures of cognitive and impulsive behavior, as well as on mood in healthy volunteers. Healthy men and women (N = 10) received placebo and 2 doses of pramipexole, 0.25 and 0.50 mg, in a within-subject, double-blinded study. Outcome measures included changes in cognitive performance, assessed by the Automated Neuropsychological Assessment Metrics, several behavioral measures related to impulsive behavior, including the Balloon Analogue Risk Task, Delay Discounting Task, Go/No-Go Task, Card Perseveration Task, and subjective ratings of mood assessed by Addiction Research Center Inventory, Profile of Mood States, and Drug Effects Questionnaire. Pramipexole decreased positive ratings of mood (euphoria, intellectual efficiency, and energy) and increased both subjectively reported sedation and behavioral sedation indicated by impaired cognitive performance on several measures of the Automated Neuropsychological Assessment Metrics. Single low to medium doses of this drug did not produce a decrease in impulsive responding on behavioral measures included in this study. The sedative-like effects observed in this study may reflect presynaptic actions of the drug. Higher doses with postsynaptic actions may be needed to produce either behavioral or subjective stimulant-like effects.

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Several lines of evidence suggest that dopamine (DA) may play an important role in impulsive behavior. Dopamine seems to be critically involved in the pathophysiology of attention deficit hyperactivity disorder, a clinical syndrome characterized by impulsive behavior and problems with attention.[1] Variants of DA receptor genes have been associated with measures of novelty seeking and impulsivity.[2] Dopamine D_2 receptor function has been associated with impulsivity and frontostriatal activity during component processes of working memory.[3] Dalley et al[4] recently reported that a form of impulsivity associated with changes in DA function in rats predicted high rates of intravenous cocaine self-administration. The psychomotor stimulants amphetamine (A) and methylphenidate, both of which increase synaptic levels of DA, are the treatments of choice for attention deficit hyperactivity disorder, and these drugs also improve performance on laboratory-based measures of impulsive behaviors in healthy volunteers.[5,6] However, the prototypic stimulant drugs have complex actions on several DA receptor subtypes and on other neurotransmitter systems. Thus, it is not known whether impulsive behaviors are specifically related to activation of particular DA receptors.

One relatively specific DA agonist that is used clinically in Parkinson's disease is pramipexole. Pramipexole binds to DA receptor subtypes within the D_2 receptor family but not to receptors of the D_1 family of receptors. Hence, it is considered to be a full intrinsic D_2 receptor family agonist, having the highest affinity for the D_3 receptor subtype and lesser affinities for the D_2 and D_4 subtypes.[7,8] Its lack of binding to D_1 family of receptors and its affinity for the D_3 receptor subtype make pramipexole unique in its pharmacological profile among the other available DA agonists. In one acute drug challenge study, Samuels et al[9] found that pramipexole caused pupil dilatation, increased heart rate, reduced prolactin and thyroid stimulating hormone, and increased growth hormone level. In an animal positron emission tomography study, pramipexole increased activity in the orbitofrontal cortex[10]—an area of the brain associated with problems in behavioral disinhibition and loss of social constraint.[11]

Impulsive behavior has been studied using several standardized behavioral measures that probably reflect different underlying dimensions of impulsivity. One dimension is delay discounting or the relative preference for immediate versus delayed rewards.[12] Delay discounting is measured using standardized procedures, including the adjusting amount delay discounting procedure developed in our laboratory.[13] Another dimension is risk taking or the tendency to engage in behaviors that entail a risk of loss. Lejuez et al[14] developed a measure of risk taking called the Balloon Analog Risk Task (BART), which we have used in our laboratory in several studies involving drug challenges.[15] In addition, the Go/No-Go procedure is a measure of responses that are successfully inhibited and is sensitive to acute drug challenge.[5] Finally, a fourth dimension that may

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relate to drug-induced impulsive behavior is the degree of persistence in games involving chance.[16,17] Vitaro et al[16] conducted a prospective study in which adolescents performed a card-playing task that involved a progressive decrease in probability of payoff. The point at which the participants stopped performing the task as the probability of rewards declined was predictive of problem gambling 3 years later.

In the present study, we examined the effects of acute doses of pramipexole on several behavioral measures that seem to reflect different dimensions of impulsivity.[15,18–20] In addition, we included several standardized measures of cognitive performance to determine the specificity of any behavioral impairments and measures of subjective mood states. We expected that low to moderate doses of pramipexole (0.25 and 0.50 mg) would decrease impulsive behavior on the tasks, similar to the effects of stimulant drugs. In addition, we hypothesized that pramipexole would negatively affect cognition and mood.

MATERIALS AND METHODS

Subjects

The participants included 10 healthy volunteers between 18 and 45 years of age. The institutional review board at the University of Chicago approved the study. Subjects were recruited from the University of Chicago and surrounding community by means of posters, newspaper advertisements, and word-of-mouth referrals. Subjects underwent an in-person psychiatric interview and a physical examination, including an electrocardiogram. They were excluded if they met criteria for major *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* diagnoses; if they had any serious cardiac, pulmonary, or liver problem; used prescription medications; had less than a high school education; had a body mass index outside the range 19 to 26 kg/m^2; or smoked more than 35 cigarettes a week. If female subjects were not taking oral contraceptives, they were scheduled during the follicular phase of their cycle. Female subjects were tested for pregnancy before each session. Before participating in the study, subjects attended an orientation session where they provided a written informed consent that stated that the study was an investigation on the effects of drugs on mood and performance and listed several drugs and possible side effects subjects may experience. For blinding purposes, they were told that they might receive a stimulant/appetite suppressant, a sedative, an antidepressant, a cannabinoid, placebo, or an anti-Parkinson's drug. Subjects also completed South Oaks Gambling Screen (SOGS)[21] and Barratt Impulsiveness Scale–11 (BIS-11).[22] They were instructed to abstain from alcohol, marijuana, or any other recreational drugs, all over-the-counter medications, and excessive caffeine and nicotine for 24 hours before and 6 hours after each session. They were also instructed to avoid driving for 12 hours after leaving the laboratory.

Design

This study used a double-blinded, placebo-controlled, within-subject design. Participants ingested a capsule containing placebo, 0.25 mg pramipexole, or 0.50 mg pramipexole in random order during 3 test sessions. They performed behavioral tasks 2.5 hours after taking the capsule, which is the approximate t_{max} for pramipexole. These low to moderate doses were selected to produce some behavioral effect while minimizing the chance of severe nausea and vomiting. The primary outcome measures were performance on measures of impulsivity and cognition.

Procedure

The study consisted of three 4-hour sessions conducted from 9 AM to 1 PM, separated by at least 72 hours. Sessions were conducted in the Human Behavioral Pharmacology Laboratory in the Department of Psychiatry at the University of Chicago Hospitals. Volunteers were tested individually in comfortably furnished rooms containing a computer for administering dependent measures, a television, and a video cassette player. During their free time, subjects were allowed to relax and engage in recreational activities such as movies or board games.

Upon arrival at 9 AM, subjects provided breath samples to ensure negative drug and pregnancy tests. Their heart rate and blood pressure were measured at this time and also every half-hour for the remainder of the session. At 9:30 AM (−30 minutes), subjects completed computerized baseline questionnaires (described in detail in "Dependent measures of mood and subjective state"). At 10:00 AM, they ingested a capsule containing either placebo, 0.25 mg pramipexole, or 0.50 mg pramipexole under double-blinded conditions. Subjective effect questionnaires and vital signs were repeated every half-hour until the completion of the study session (+30, +60, +90, +120, +150, +210 minutes). At 12:30 PM (+150 min), subjects completed the cognitive and behavioral tasks (see below). They then completed an end-of-session questionnaire assessing their test-day experience. After completing all 3 sessions, subjects attended a debriefing session, at which time they were paid, and the study was explained in detail.

Drugs

Pramipexole (0.25 or 0.50 mg Mirapex) was administered in green gelatin capsules (size 00) with dextrose filler. Placebo capsules contained only dextrose. These low to moderate doses of pramipexole were selected to produce measurable effects on behavior without unpleasant side effects.[23] These doses have been used clinically to improve mood disorders,[24] and they are within the therapeutic range.

Dependent Measures of Impulsivity

Delay Discounting

This task uses a computerized adjusting amount procedure to measure discounting of delayed and uncertain reinforcers.[13] Subjects have the opportunity to choose between different amounts of money available after different delays or with different probabilities. The test consists of approximately 110 questions such as (1) Would you rather have $10.00 in 30 days or $2.00 at the end of the session or (2) Would you rather have $5.00 for sure or $10.00 with a 25% chance? The indifference points obtained at each of the

delays and probabilities are then plotted to form 2 discount functions. The delay discounting function is derived through curve-fitting analyses, which yield a value for the parameter *k*: higher values of *k* are taken to indicate greater impulsivity. Similar procedures are used to derive the probability discounting function.

Balloon Analogue Risk Task

The BART is a measure of risk taking in which participants can earn or lose points redeemable for money.[14,25] Participants "pump up" a balloon presented on a screen by clicking a computer mouse. For each pump, a counter on the screen increases by a certain amount of money (1, 5, or 25 cents). After an unpredictable number of "pumps," the balloon may "explode," resulting in a loss of the money accumulated in the counter. Participants who emit more pumps are considered more impulsive.

Go/No-Go Task

This is a test of learning that is designed to assess the ability to inhibit an inappropriate response.[26] It also provides a measure of relative sensitivity to reward and response cost (loss). The task consists of repeated presentations of 8 pairs of numbers, of which 4 are designated "correct," and 4 are "incorrect." The subject's task is to respond to the correct numbers and to withhold responses to the incorrect numbers. The outcome measures are errors of omission (withholding a response when a "correct" stimulus is presented) and errors of commission (responding to an "incorrect" stimulus). Impulsive individuals are expected to exhibit more errors of commission.

Card Perseveration Task

This card-playing task is designed to measure "response perseveration" or the tendency to persist in making previously rewarded responses that have become maladaptive (ie, punished).[27] The task is a probability learning game in which the punishment-reward ratio changes as the game proceeds; specifically, the probability of punishment increases linearly with the progression of the game.

Dependent Measures of Cognition

Automated Neuropsychological Assessment Metrics (ANAM) were used to detect changes in cognitive function (knowing, thinking, learning) after drug administration.[28] The ANAM was developed by the Department of Defense to detect impairments in visual-spatial problem solving, working memory, and mental efficiency measures. We used 2 specific tasks from the ANAM: (1) simple reaction time—a large asterisk-like symbol appears on the monitor screen at variable time intervals, and subjects are required to press a mouse button as quickly as possible; and (2) procedural reaction time—subjects are asked to press the left side of the mouse when they see numbers 2 and 3 and press the right side of the mouse when they see numbers 4 and 5. Reaction time is recorded, as well as the number of lapses or times the subject fails to respond on a trial. Accuracy for simple reaction time is found by dividing the number of correct responses by the number of correct responses plus the number of lapses. Accuracy for procedural reaction time is calculated by dividing the number of correct responses by the number of correct responses plus the number of incorrect responses plus the number of lapses.

Dependent Measures of Mood and Subjective State

Addiction Research Center Inventory

The Addiction Research Center Inventory (ARCI) is a standardized measure of drug effects.[29–31] The questionnaire consists of 53 true/false statements describing subjective effects of various classes of abused drugs. The version of the ARCI used in this study consists of 6 empirically derived scales that measure drug-induced euphoria (morphine-benzedrine group [MBG]), stimulant-like effects (A, intellectual efficiency and energy (benzedrine group [BG]), sedation (pentobarbital-chlorpromazine alcohol group [PCAG]), dysphoria and somatic effects (lysergic acid), and marijuana-like effects.

Profile of Mood States

The Profile of Mood States (POMS)[32] is an adjective checklist that is sensitive to the effects of psychoactive drugs.[33,34] We use a version of the POMS consisting of 72 adjectives commonly used to describe momentary mood states. Subjects indicate how they feel at the moment in relation to each of the 72 adjectives on a 5-point scale from "not at all" (0) to "extremely" (4). Eight clusters (scales) of items have been separated empirically using factor analysis (anxiety, depression, anger, vigor, fatigue, confusion, friendliness, elation). The value of each scale is determined by averaging the scores for the adjectives in that cluster. Two additional (nonvalidated) scales are derived from the other scales as follows: arousal = (anxiety + vigor) − (fatigue + confusion); positive mood = elation − depression.

The Drug Effects Questionnaire

The Drug Effects Questionnaire (DEQ) measures the subjective states "feel drug," "feel high," "like drug," and "want more."[35] Subjects indicate on a 100-mm line the extent to which they feel each statement ranging from "not at all" on the left of the scale to "extremely" on the right end of the scale.

The End-of-Session Questionnaire

Subjects were asked to identify the substance they thought they received (stimulant/appetite suppressant, a sedative, an antidepressant, a cannabinoid, placebo, or an anti-Parkinson's drug) and to rate on a 100-mm line how much they liked its effects. They were also allowed to comment on any unusual effects they experienced and whether they would take the substance again.

Personality Questionnaires

The BIS-11

The BIS-11 was used to assess impulsivity as a personal trait.[22] The questionnaire consists of 30 statements

TABLE 1. Effects of Pramipexole on the Simple Reaction Time and Procedural Reaction Time

Measure	Placebo	Pramipexole 0.25 mg	Pramipexole 0.50 mg
Simple reaction time			
Median reaction time (ms)	322.8 ± 12.07	359.4 ± 19.4*	375.4 ± 19.1*
No. lapses	0 ± 0	1.6 ± 1.2	2.0 ± 1.4
Accuracy (%)	100 ± 0	98.4 ± 3.9	98.0 ± 4.5
Procedural reaction time			
Median reaction time (ms)	587.1 ± 33.48	620.8 ± 23.1	659.9 ± 36.4*
No. lapses	1 ± 0.6	1.9 ± 1.2	2.3 ± 1.1
Accuracy (%)	94 ± 6.5	90.6 ± 8.7	89.6 ± 9.4

Data represent mean of median reaction time scores on placebo and pramipexole sessions.

*Significant differences ($P \leq 0.05$) between placebo and the corresponding pramipexole dose (Student paired-samples *t* test).

to which subjects respond by choosing 1 of the following responses: rarely/never, occasionally, often, and almost always.

South Oaks Gambling Screen

This questionnaire was administered to collect data on individual differences.[21] The instrument consists of 20 items, and the scores range from 0 to 20. A score of 3 or 4 indicates a potential gambling problem, and a score of 5 or higher indicates a probable pathological gambling problem. The SOGS has been the most widely used instrument in assessing the prevalence of pathological gambling among the general public.

Data Analysis

Data analyses were conducted using SPSS (version 14.0; SPSS, Chicago, Ill). Two-way, repeated-measure analyses of variance (ANOVA) were used to examine the effects of drug (3 levels: placebo, 0.25, and 0.50 mg pramipexole) over time (baseline, +30, +60, +90, +120, +150, +210) for subjective measures. Data for DEQ, Go/No-Go, Card Perseveration Task, and ANAM were analyzed using 1-way ANOVAs (3 levels: placebo, 0.25, and 0.50 mg pramipexole), and data from BART were analyzed using 2-way ANOVA (3 levels: placebo, 0.25, and 0.50 mg pramipexole) over the value of the balloon (1, 5, and 25 cents). Post hoc *t* tests with Bonferroni correction factor were used to account for multiple comparisons with the placebo condition. The reaction time data for ANAM were analyzed as means of the median values for each subject. The significance level for all statistical tests was $P < 0.05$.

RESULTS

Subject Demographics

Subjects ranged in age from 18 to 28 years. All subjects were either attending college at the time of the study or had a college degree. Nine subjects scored 0 on the SOGS, and 1 subject scored 3, indicating some problems with gambling. The possible range of scores on the SOGS are 0 to 20.

Cognition

Both doses of pramipexole significantly impaired performance on ANAM. Pramipexole (0.25 and 0.50 mg) significantly increased reaction times on the Simple Reaction Task in a dose-dependent manner. Pramipexole (0.50 mg) significantly increased reaction time on the procedural reaction time. The drug also slightly increased the number of lapses (ie, decreased accuracy) on both the simple reaction and procedural reaction times, but these increases did not reach significance. The results are summarized in Table 1.

Impulsivity

Pramipexole did not significantly affect either delay or probability discounting. Two subjects were omitted from this analysis because their data did not fit the hyperbolic function (r^2 values were negative). The r^2 values for log k were 0.88, 0.62, and 0.71. On the probability discounting task, only 1 subject's data were excluded because of negative r^2 values. The r^2 values for log h were 0.93, 0.88, and 0.85. Figure 1 shows the mean indifference points for these subjects.

Pramipexole did not affect performance on the Card Perseveration Task or the BART. The range of the number of cards played and the mean number of cards played were placebo, 16 to 73 (mean, 40.1); 0.25 mg pramipexole, 19 to

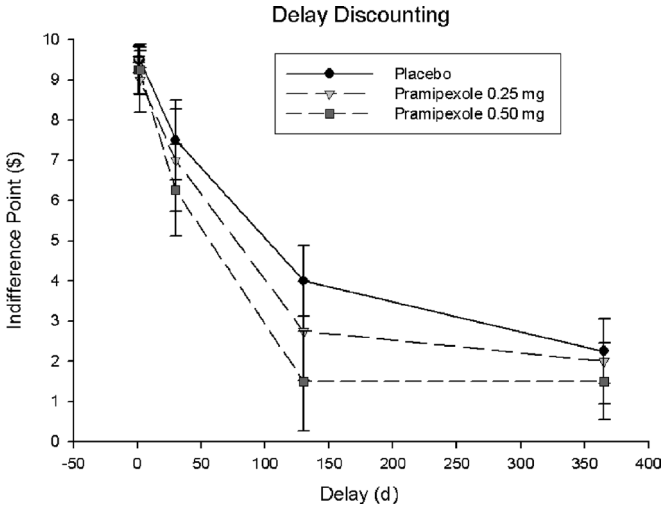

FIGURE 1. Mean (±SEM) in difference points for delay discounting after placebo, 0.25, and 0.50 mg pramipexole. Pramipexole did not significantly affect delay discounting.

TABLE 2. Effects of Pramipexole on the Go/No Go Task

Measure	Placebo	0.25 mg Pramipexole	0.50 mg Pramipexole
False alarm/total error	0.84	0.94	0.98
Reaction time (ms)	694.8 ± 30.9	675.0 ± 43.8	640.9 ± 37.9
Reaction time after a false alarm (ms)	630.4 ± 34.7	558.9 ± 47.1	518.5 ± 40.1
Reaction time after a hit (ms)	669.2 ± 45.8	668.6 ± 50.3	610.5 ± 37.5

Data represent mean ± SEM of placebo and pramipexole sessions.

95 (mean, 45.5) and 0.50 mg pramipexole, 26 to 65 (mean, 39.6). In addition, pramipexole did not significantly impact performance on the BART.

Pramipexole (0.25 and 0.50 mg) did not affect performance on the Go/No-Go task. Data from 2 subjects were lost due to error. The drug did not affect either errors of omission or errors of commission in the remaining 8 subjects. The most concise outcome measure for the Go/No-Go task is the ratio of false alarms to all errors. Although this ratio increased in a dose-dependent manner, it did not reach statistical significance. The reaction times decreased as the doses of pramipexole increased but also did not reach the statistical significance (Table 2).

Subjective Effects

Pramipexole significantly increased subjective ratings of sedation as measured by the PCAG scale of the ARCI and decreased ratings of euphoria and intellectual efficiency and energy as measured by the MBG and BG scales of the ARCI, respectively. Post hoc analyses revealed that the 0.50-mg dose decreased scores on the MBG and BG, relative to placebo, after 210 minutes. As shown in Figure 2, the 0.50-mg dose increased the ratings of sedation on ARCI scale relative to placebo at 150 and 210 minutes. In addition, 0.50 mg pramipexole significantly decreased ratings of vigor compared with placebo at 210 minutes and decreased the ratings of positive mood relative to placebo at 120, 150, and 210 minutes. Pramipexole (0.50 mg) also significantly decreased the ratings of "like" on the DEQ scale at 210 minutes.

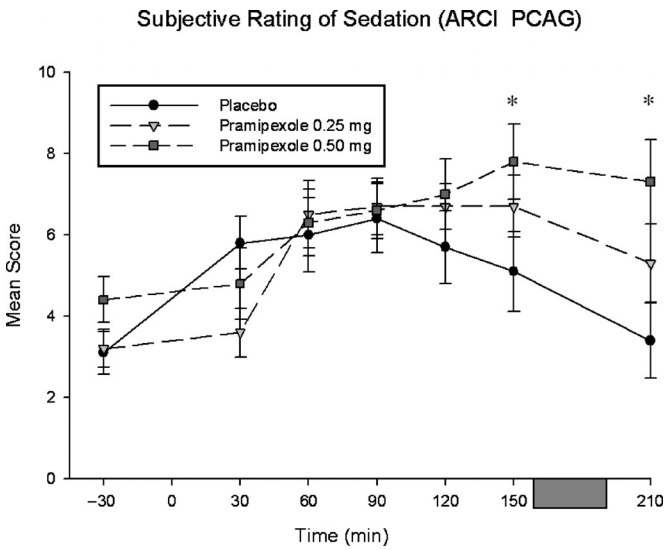

FIGURE 2. Mean (±SEM) scores for subjective sedation (ARCI PCAG scale) for placebo (circles), 0.25- (triangles), and 0.50-mg pramipexole (squares) sessions at baseline (−30) and repeated times after capsule ingestion. The shaded region along the *x* axis shows when the impulsivity tasks were performed, coinciding with the time of peak drug effects. * indicates significant ($P \leq 0.05$) differences between 0.5 mg pramipexole and placebo at 150 and 210 minutes.

Personality Data

The mean score on the BIS-11 was 63.4 ± 7.152. Using a comparable population, this value is similar to the mean value reported by Barratt in the development of the scale.[22] The mean SOGS score was 0.3 ± 0.949. There were not enough subjects or enough variability in the data to examine the effects of pramipexole on the tasks in relation to trait levels of impulsivity.

DISCUSSION

The primary goal of this study was to determine how low to moderate doses of pramipexole affect cognition and impulsivity in healthy volunteers. Contrary to our expectations, pramipexole did not reduce impulsive behavior. Because pramipexole has a high affinity for D_3 receptors, the findings of this investigation suggest that the dimensions of impulsivity included in this study are not mediated through this subfamily of DA receptors. Rather, the drug significantly impaired cognitive performance and produced sedative-like subjective effects. Although our results were not expected based on similarities to prototypic stimulant drugs, our results are consistent with the results of another recent study in healthy volunteers in which pramipexole (0.50 mg) reduced both subjective alertness and alertness measured with critical flicker fusion and also decreased pupillary light response.[9]

The sedative-like effects of the D_3 DA agonist and its performance-impairing effects may be related to presynaptic autoreceptor actions. In a study on the effects of pramipexole on the noradrenergic locus coeruleus (LC),[9] low doses of pramipexole activated presynaptic DA D_2 autoreceptors located in the ventral tegmental area. As the ventral tegmental area projects to the LC, a major wakefulness-promoting nucleus, pramipexole, in essence "turns off" the excitatory effect of LC, thereby reducing alertness.[36,37] The sedative-like effects observed in this study may reflect presynaptic actions of the drug. Higher doses with postsynaptic actions

may be needed to produce either behavioral or subjective stimulant-like effect.

In the present study, we used relatively low to moderate doses of the drug within the clinical dose range of 0.125 to 1.50 mg per dose. It was not possible for us to increase the dose further because of severe nausea associated with higher doses of pramipexole. Indeed, in our study, 1 subject experienced nausea on the 0.25-mg dose, whereas 5 of the 10 subjects experienced nausea on the 0.50-mg dose. We also tested several additional subjects with a 1.0-mg dose in combination with the antiemetic drug trimethobenzamide, but it was not possible to block the drug-induced emesis and nausea. Thus, the possibility remains that acute high doses of pramipexole may decrease impulsive behaviors in healthy volunteers, but this idea cannot be feasibly tested because of the emetic effects of the drug.

An alternative explanation for the lack of effect of pramipexole is that the tasks used in this study may not be sensitive to detect behavioral effects of the drug. Some of the tasks selected for the present study have been shown in previous laboratory studies to be sensitive to the effects of acute drug administration, and they are considered to be valid measures of impulsive behavior.[38] For example, we reported that D-amphetamine decreased the number of errors of commission (ie, false alarms) relative to placebo on the Go/No-Go task.[5] In addition to being sensitive to the effects of psychotropic drugs, the tasks used in this study are also sensitive to the population studied.

The main findings of this study are that low to moderate doses of pramipexole impaired cognition and produced sedative subjective effects and nausea in healthy young adults. Unlike the effects of stimulant drugs, pramipexole did not produce a decrease in impulsive responding on behavioral measures included in this study. It remains to be determined whether higher doses of the drug or multiple repeated doses over a longer period might produce a different profile of behavioral effects.

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