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Pergolide Treatment of Cognitive Deficits Associated with Schizotypal Personality Disorder: Continued Evidence of the Importance of the Dopamine System in the Schizophrenia Spectrum

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Cognitive deficits observed in schizophrenia are also frequently found in individuals with other schizophrenia spectrum disorders, such as schizotypal personality disorder (SPD). Dopamine appears to be a particularly important modulator of cognitive processes such as those impaired in schizophrenia spectrum disorders. In a double-blind, placebo-controlled clinical trial, we administered pergolide, a dopamine agonist targeting D_1 and D_2 receptors, to 25 participants with SPD and assessed the effect of pergolide treatment, as compared with placebo, on neuropsychological performance. We found that the pergolide group showed improvements in visual-spatial working memory, executive functioning, and verbal learning and memory. These results suggest that dopamine agonists may provide benefit for the cognitive abnormalities of schizophrenia spectrum disorders.
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INTRODUCTION

Impaired cognition is a core feature of schizophrenia (Green, 2006). Cognitive deficits, which are found in at least 75–85% of patients (Reichenberg *et al*, 2006), typically precede the onset of other symptoms (Sørensen *et al*, 2006) and persist after other symptoms have been effectively treated (Heinrichs, 2005). Cognitive deficits are the single best predictor of functional outcome in schizophrenia (Bozikas *et al*, 2006; Hofer *et al*, 2005; Milev *et al*, 2005). They predict poorer medication (Burton, 2005) and treatment (Prouteau *et al*, 2004) adherence, reduced adaptive and social skills (Bowie and Harvey, 2005), dysfunctional personality traits (Gurrera *et al*, 2005), and increased risk of relapse in first-episode patients (Chen *et al*, 2005). The cognitive dysfunction of schizophrenia appears to involve almost all the known neurotransmitter systems (Tamminga, 2006) and is also be found in probands' non-schizophrenic relatives (Keefe *et al*, 1994; Sitskoorn *et al*, 2004).

Substantial research has implicated the dopaminergic system as a modulator of cognitive processes, particularly those subserved by the pre-frontal cortex (PFC), striatum, and associative structures (Cropley *et al*, 2006). A positive correlation between PFC D_1 receptor alteration and cognitive impairments was initially reported in animal studies. Primate research has also consistently found that the natural aging process is associated with deterioration in the parameters of dopamine receptor signaling (Goldman-Rakic and Brown, 1981; Hemby *et al*, 2003; Naoi and Maruyama, 1999) and the emergence of impairments in working memory and executive functions (Volkow *et al*, 1998). Enhancement of working memory in aged monkeys is observed after D_1 receptor signaling boost with D_1 agonist treatment (Castner and Goldman-Rakic, 2004), and performance deficits in spatial working memory tasks can be pharmacologically reversed in DA-deficient monkeys and rats after dopamine D_1 agonist administration (Arnsten *et al*, 1994; Castner *et al*, 2000; Castner and Goldman-Rakic, 2004). Furthermore, pharmacological modulation of working memory impairment through use of a D_1 agonist in antipsychotic-treated monkeys shows lasting benefit 1 year later (Sawaguchi and Goldman-Rakic, 1991; Brozoski *et al*, 1979).

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In humans, dopamine has been implicated in the cognitive dysfunction observed in a variety of neuropsychiatric disorders including Parkinson's disease (White, 1996; Owen and Robbins, 1998; Lange *et al*, 1992; Lewis *et al*, 2005), Huntington's disease, traumatic brain injury and stroke (McDowell, 1996), attention-deficit/hyperactivity disorder (Dinn *et al*, 2001; Shallice *et al*, 2002), and schizophrenia (Davis *et al*, 1991; Goldman-Rakic, 1999) and spectrum disorders (Trestman *et al*, 1995; Roitman *et al*, 2001). Therefore, pharmacological interventions targeting the dopamine system, and in particular D_1 receptors, are a logical choice for treating the widespread cognitive dysfunction found in schizophrenia patients. However, there are several important challenges in examining the effect of dopamine modulation in this population, such as potential interactions with antipsychotic medication (Harvey and McClure, 2006).

Multiple cognitive abilities are impaired in people with schizotypal personality disorder (SPD), in a profile similar to that found in individuals with schizophrenia. Individuals with SPD show impairment as great as individuals with schizophrenia on tests using working memory (Heinrichs and Zakzanis, 1998; Mitropoulou *et al*, 2002, 2005). Impairments in episodic learning and memory are among the most widely replicated and pronounced cognitive deficits in schizophrenia (Saykin *et al*, 1991) and are also impaired in SPD in both verbal (Dickey *et al*, 2005) and visual-spatial modalities (McClure *et al*, 2007b). Thus, SPD patients show cognitive deficits that are similar to what is found in many individuals with schizophrenia, but these impairments are slightly reduced in severity and SPD patients are largely free from the potential confounds found in samples of schizophrenia patients.

In this study, we sought to examine the effectiveness of pergolide, an agonist at both D_1 and D_2 receptors, for the treatment of cognitive abnormalities of individuals with SPD. Although pergolide is more potent at the D_2 receptor, pergolide has a strong D_1 receptor affinity and one of the most potent physiological effects at D_1 receptor of the clinically available dopamine agonists (Gibbs and D'Esposito, 2006; Kimberg and D'Esposito, 2003; Müller *et al*, 1998). During the course of this study, concerns regarding the possibility of increased valvular heart disease in patients treated with ergot-derived dopamine agonists such as pergolide arose (Schade *et al*, 2007; Zanettini *et al*, 2007). Although none of the participants in this cohort had experienced any adverse effects from pergolide, because of these concerns we decided to suspend recruitment after enrolling 25 participants.

Pergolide has been shown to improve working memory in humans (Kimberg and D'Esposito, 2003), although it has not been previously administered to individuals in the schizophrenia spectrum. However, as we have previously found that the cognitive abnormalities of individuals with SPD were improved with pharmacological intervention (McClure *et al*, 2007a), we hypothesized pergolide would be an effective treatment for cognitive deficits observed within the schizophrenia spectrum. Specifically, we predicted that individuals with SPD who were treated with pergolide, compared with those treated with placebo, would show improved performance on neuropsychological tasks related to dopamine functioning, which includes a variety of measures of attention and working memory.

MATERIALS AND METHODS

Participants

We recruited male or female participants between the ages of 18 and 60 years from the outpatient clinics at the Mount Sinai Medical Center (New York, NY) and the James J Peters Veterans Affairs Medical Center (Bronx, NY). Participants were required to meet *DSM-IV* criteria for SPD while those who met current or lifetime *DSM-IV* criteria for schizophrenia or any schizophrenia-related psychotic disorder or for bipolar disorder were excluded. All participants were without abuse of illicit substances or alcohol within the past 6 months or a past history of substance dependence. All participants had been free of psychotropic medication for at least 2 weeks. All patients received a urine toxicology screen. See our previous publications for the full diagnostic assessment process. The study was approved by the institutional review boards of the Mount Sinai School of Medicine and the James J Peters Veterans Affairs Medical Center, and all participants signed a written informed consent statement after the study was explained to them.

Treatment Design

The placebo-controlled double-blind trial lasted for 4 weeks. Participants were randomized to receive either placebo or active drug and the dosage of pergolide was titrated upward in a stepwise design. The active drug group received 0.025 mg/day for the first 3 days, 0.05 mg/day for days 4 through 7, 0.1 mg/day for week 2, 0.2 mg/day for week 3, and 0.3 mg/day for week 4. The maximum dose was based on previous research (Müller *et al*, 1998) and pilot data indicating that a dose of 0.3 mg per day provided greater benefit than lower doses but was not enough to cause side effects in most participants. Participants were assessed at baseline and after 4 weeks of treatment.

Cognitive Assessments

DOT test. The DOT test is an assessment of visuospatial working memory in wide research use (Keefe *et al*, 1995, 1997). Subjects are presented a dot at a specific position on a standard size paper and then asked to reproduce it at the same location on a separate sheet after different periods of delay (no delay, 10, 20, or 30-s delay). The distance error at the 30-s delay minus the distance error at the immediate condition was the dependent variable of interest in this study.

Paced auditory serial addition test (PASAT). The PASAT is a test of auditory verbal working memory that has been well described and validated in this population (Gronwall, 1977; Stuss *et al*, 1988). Briefly, subjects listen to a tape-recorded voice presenting a series of numbers (50 numbers at a rate of one digit per 2 s) and are asked to add each adjacent pair of numbers and respond by verbalizing the sum. The total number of correct responses is the dependent variable.

Wechsler memory scale visual reproduction test (WMS-VR). The WMS-VR is a measure of memory for non-verbal stimuli (Wechsler, 1987). Four line drawings are presented one at a time for a 10-s exposure period. After the drawing is removed, the subject is asked to immediately draw the figure from memory. Participants are then asked to draw the four items from memory after a 30-min delay, with no prompts or cues provided. The raw score of the visual reproduction of the four figures after this delay is the dependent variable.

Word list learning (WLL). The WLL test used in this study is an assessment of verbal learning and memory developed for use in clinical trials. Participants are presented with one of five matched lists of 25 words over five learning trials and are then presented with a distractor list. Participants are asked to recall the initial list immediately and after a 20-min delay. The total number of words recalled over the five learning trails and the number of words recalled at the 20-min delay interval were the dependent variables.

N-back working memory task (N-back). The N-back is a commonly used measure of working memory (Braver *et al*, 1997; Casey *et al*, 1995) that has been frequently shown to elicit performance deficits among individuals with schizophrenia and their unaffected relatives (Barch *et al*, 2002; Braver *et al*, 1997). Participants observed letters presented on a computer screen one at a time over three conditions: (1) 0-back, (2) 1-back, and (3) 2-back. In the 0-back condition, participants responded to a single pre-specified target letter (eg, X). In the 1-back condition, the target was any letter identical to the one immediately preceding it (ie, one trial back). In the 2-back condition, the target was any letter identical to the one presented two trials back. For this study, the dependent variable was the number of correct responses for the 2-back condition.

Letter-number span (LNS). This test requires subjects to listen to a list of intermingled letters and numbers. At the end of the presentation of the stimuli, subjects are asked to reproduce the information with the numbers in ascending order and the letters in alphabetical order, with numbers coming first. The number of correct trials served as the dependent variable.

Trail-making test (TMT). TMT has two conditions that combine to assess verbal/spatial perception and psychomotor speed (Reitan and Wolfson, 1993). In Part A, the subject must connect numbers presented on a standard sheet of paper in ascending order (1–2–3). In Part B, the subject must alternate connecting numbers and letters (eg, 1-A, 2-B, 3-C, and so on). The amount of time to complete Part A and Part B were the two dependent variables.

AX-CPT task. Participants performed three conditions of the AX-CPT: standard, degraded, and interference. Sequences of letters were visually presented one at a time in a continuous manner on a computer display. Participants were instructed to make an affirmative response on target trials and a negative response otherwise (for a full description, please see Barch *et al*, 2004). The delay between cue and probe was manipulated, so that half of the trials had a short delay and half had a long delay. On short-delay trials, the cue-probe interval was 1 s, and the inter-trial interval was 4900 ms. On long-delay trials, the cue-probe interval was 5 s and the inter-trial interval was 1 s. Thus, the total trial duration was equivalent across conditions, providing a means of controlling for general factors that might affect performance (eg, pace of the task, response frequency, and total time on task). The task was presented in four blocks of 50 trials, all of which were either short- (two blocks) or long- (two blocks) delay trials, with the order of short- and long-delay blocks counterbalanced across subjects. Participants were asked to respond as quickly as possible to each stimulus while maintaining accuracy. For this study, we used the interference version of the AX-CPT, during which an interference stimulus is presented between the cue and the probe, thereby increasing the difficulty of the task. The critical dependent variables used in this study were BX errors after a short-delay interval and AY errors after a long-delay interval.

Data Analysis

We calculated difference scores (post-treatment minus baseline scores) for each of our neuropsychological measures and computed a multivariate analysis of variance with these difference scores serving as the dependent variables (WLL results were excluded from this analysis because of a large amount of missing data for this test). We then computed a series of one-way ANOVAs comparing the pergolide and placebo groups, with each of these difference scores serving as the dependent variables for the two-group comparison. To control for baseline levels of impairment, we entered the participants' baseline scores into each model as a covariate. In addition, a Sidak correction for multiple comparisons was carried out for all ANOVAs.

RESULTS

In total, we enrolled 25 participants. One participant discontinued participation in the study after week 2, leaving 12 participants randomized to pergolide and 12 randomized to placebo. The groups were comparable on age, $t(22) = 0.334$, $p = 0.74$, and education, $t(22) = 0.694$, $p = 0.50$, and all participants were right-handed (See Table 1 for demographic characteristics). There was a significant difference in the gender composition of the groups, $\chi^2(1) = 5.04$, $p < 0.05$, as there were fewer females in the placebo group; however, when groups were collapsed and the baseline performance of male participants was compared with that of female participants, there were no significant differences on any of our assessments. In addition, all but two participants, one from each group, were naïve to antipsychotic medication; one of these participants had taken stelazine for a few years beginning in 1972 and the other had taken imipramine and thorazine during a brief hospitalization several years before enrollment in the study.

Raw scores on our measures are presented in Table 2. Overall, the results of our MANOVA were statistically significant, $F(1, 9) = 14.63$, $p = 0.006$, suggesting that there

was a difference between the groups after treatment with either pergolide or placebo. Furthermore, we found that individuals with SPD treated with pergolide showed statistically significant improvement, compared with those in the placebo group, on several tasks that are hypothesized to be related to the activity of dopamine (See Table 2). Specifically, verbal learning and memory improved with pergolide compared with placebo for both the immediate and delayed recall intervals of the WLL test. Furthermore, when compared with the placebo group, the pergolide group showed improvement on the verbal working memory as measured by LNS performance. The pergolide group also showed improvement on the TMT Part B, a measure of executive functioning, when compared with the placebo group. In addition, individuals treated with pergolide, compared with those given placebo, showed significant improvement in long-term visual-spatial memory, as measured by the *WMS-VR* delayed recall score. Individuals treated with pergolide also showed a significant improvement in visual-spatial working memory, as measured by the DOT test, although this was largely driven by a worsening in performance of individuals in the placebo group not observed in individuals in the pergolide group.

Results for our modified version of the AX-CPT were somewhat mixed. Contrary to our hypotheses, we did not observe a statistically significant difference between the pergolide group and the placebo group for AY errors after a long delay. Although there was a statistically significant difference between groups for BX errors after a short delay, these results should be interpreted with caution. Our pergolide group showed the expected decrease in BX errors after treatment; however, the placebo group, which had an unusually high number of BX errors at baseline, also showed a decrease in these types of errors. Thus, we cannot

Table 1 Sample Characteristics

	Group					
	Pergolide			Placebo		
	M	SD	Range	*M*	SD	Range
Age	37.42	11.66	12–60	41.18	11.00	25–58
Sex (% males)	91			50		
Education (years)	14.75	2.63	11–19	14.82	2.14	12–18

Table 2 Means and Difference Scores for the Cognitive Assessments by Group

	Pergolide group		Placebo group		*F* (*p*)	Effect size[a]
	Baseline *M* (SD)	Change score *M* (SD)	Baseline *M* (SD)	Change score		
Visual-spatial working memory						
DOT test—30 s delay	1.13 (0.83)	0.10 (1.03)	1.30 (0.93)	−0.74 (2.17)	3.90 (0.04)	0.92
N-back (2-back)	0.79 (0.08)	0.05 (0.07)	0.80 (0.09)	0.01 (0.14)	2.49 (0.12)	0.52
Verbal working memory						
Letter number span	15.33 (3.2)	1.83 (2.25)	13.91 (3.44)	0.00 (1.26)	4.23 (0.03)[b]	0.57
PASAT	34.25 (11.81)	5.25 (7.30)	30.50 (12.36)	8.08 (8.51)	1.85 (0.18)	−0.21
Visual-spatial long-term memory						
WMS delayed recall	30.25 (7.02)	1.75 (7.06)	28.50 (8.95)	1.25 (5.97)	4.53 (0.02)	0.11
Verbal memory						
WLL immediate recall	16.00 (4.55)	5.43 (16.16)	14.00 (5.24)	3.33 (16.93)	4.21 (0.04)	0.55
WLL delayed recall	16.57 (5.10)	3.00 (2.0)	14.00 (5.05)	0.11 (2.67)	6.76 (0.01)[b]	0.57
Context processing						
AX-CPT BX short delay	0.15 (0.22)	−0.11 (0.20)	0.35 (0.45)	−0.08 (0.53)	8.53 (0.01)	−0.32
AX-CPT AY long delay	0.10 (0.11)	−0.03 (0.24)	0.05 (0.13)	−0.16 (0.15)	0.99 (0.39)	0.96
Executive functioning						
TMT Part B (s)	83.42 (34.06)	31.75 (39.61)	100.25 (43.48)	15.45 (33.34)	6.88 (0.005)[b]	0.57
Processing speed						
TMT Part A (s)	28.08 (8.95)	−1.50 (26.36)	34.25 (8.08)	0.07 (9.02)	0.33 (0.73)	−0.17

[a]Effect size of the pergolide group minus effect size of the placebo group.
[b]Indicates a statistically significant difference in performance between the pergolide and placebo groups following a Sidak correction for multiple comparisons.

determine whether the effect of pergolide on the BX error frequency also reflected some tendencies of regression to the mean such as was observed in the placebo group.

To evaluate whether the results were influenced by the number of statistical tests performed, we re-ran the ANOVAs using a Sidak correction for multiple comparisons; using this correction, only LNS, WLL Delay, and Trails B remain significant. Thus, although there were a number of influences of pergolide on cognition, the corrected results indicate that three cognitive domains were beneficially affected.

DISCUSSION

This study was an examination of the effectiveness of pergolide for the treatment of cognitive deficits of individuals with SPD, a schizophrenia spectrum illness. A significant body of evidence suggests that the neurotransmitter dopamine has an important role in many cognitive functions. D_1 receptors in particular appear to be related to both healthy cognitive functioning and cognitive abnormalities observed in many psychiatric illnesses such as schizophrenia. At this time, there are no selective D_1 agonists available for use in humans. However, although pergolide primarily targets D_2 receptors, it has a very high D_1 receptor affinity.

As we predicted, SPD participants treated with pergolide showed an improved performance on a number of neuropsychological assessments, even after correction for multiple comparisons. In particular, processing speed, executive function/working memory, and verbal learning and memory improved after 4 weeks of pergolide treatment. In addition, participants treated with pergolide performed significantly better on one of our measures of verbal working memory and one of our measures of visual-spatial working memory. It should be noted, however, that although there was a significant difference between groups for our measure of visual-spatial long-term memory, there was a very small effect size for this difference. Although analyses of two other measures of working memory were not statistically significant, in both cases examination of mean scores suggests that there was an improvement for the pergolide group. There was evidence of some practice effects in the placebo group, but the parallel nature of this design means that greater improvements in patients randomized to pergolide could not be attributed solely to practice. Pergolide did not improve performance on a measure of processing speed, meaning that the other findings are not likely because of a stimulant-like effect of pergolide. The small sample size is a limitation of the design, but robust improvements in cognitive functioning in several domains were detected despite the small size of the study.

We also failed to observe an improvement in the context processing of individuals treated with pergolide, compared with those treated with placebo. In the past, we have found that AX-CPT performance of individuals with SPD was amenable to pharmacological intervention with guanfacine (McClure *et al*, 2007a). This is a small-scale study and the results must be viewed accordingly, which may mean that the baseline scores were unstable because of the small sample size. The effect of other dopamine agonists on context processing is an area that has been studied previously (Barch and Carter, 2005), and other dopaminergic agents merit investigation in this area as well.

Although this study was in progress, concerns were raised regarding the possibility of increased valvular heart disease in patients treated with ergot-derived dopamine agonists such as pergolide (Zanettini *et al*, 2007; Schade *et al*, 2007), which caused us to suspend recruitment after only 25 participants had been enrolled. Although pergolide has subsequently been removed from the market, the results of our study are promising and suggest that dopamine agonists that specifically target D_1 receptors are in fact effective in ameliorating cognitive deficits such as those observed in SPD and schizophrenia. As cognitive abnormalities are closely linked to the functional outcomes of this population, the results are important for furthering the recovery of individuals with schizophrenia spectrum illnesses. Identifying a safe D_1 agonist for use in human samples, therefore, is an avenue of future research that is vital for promoting recovery.

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DISCLOSURE

In the last 3 years Dr Harvey has served as a consultant for: Eli Lilly and Company, Johnson and Johnson, Pfizer, Solvay-Wyeth, The Sanofi-Aventis Group, Neurogen, and Daimippon Sumitomo America. Dr Harvey has grant support from Astra-Zeneca Pharmaceuticals. Dr Koenigsberg had grant support from Janssen Pharmaceuticals. The remaining authors declare that, except for income received from their primary employers, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

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