A Pilot Study of Adjunctive Atomoxetine Treatment to Second-Generation Antipsychotics for Cognitive Impairment in Schizophrenia

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Abstract: Relationships between altered prefrontal cortical dopamine, norepinephrine, and some of the cognitive impairments of schizophrenia support an approach for pharmacological remediation of cognitive symptoms through manipulations of prefrontal cortical dopamine and norepinephrine. Atomoxetine, a selective norepinephrine reuptake inhibitor, produces a widespread increase in brain norepinephrine and a secondary and selective increase in prefrontal dopamine. Given this, we evaluated atomoxetine's cognitive effects in a pilot placebo-controlled trial in patients with schizophrenia. Moreover, a functional magnetic resonance imaging investigation was undertaken to assess the neural mechanisms underlying the cognitive effects of atomoxetine. Twenty participants with schizophrenia were randomized to treatment with placebo or atomoxetine 80 mg daily for an 8-week parallel-designed treatment trial. Cognitive performance was assessed with the Brief Assessment of Cognition in Schizophrenia. No significant cognitive improvement was associated with atomoxetine treatment. However, atomoxetine treatment was associated with significantly greater increases in working memory-related activation of the left dorsolateral prefrontal and left posterior cingulate cortices. The negative results of this study conflict with the effectiveness of amphetamine in enhancing the cognitive abilities of schizophrenic patients and may be related to the differential pattern of cortical activation and deactivation produced by amphetamine.

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There is a great deal of evidence implicating the prefrontal cortex (PFC) in cognitive functions relevant to schizophrenia.[1] Moreover, evidence for relationships between altered PFC dopamine (DA), norepinephrine (NE), and some of the cognitive impairments of schizophrenia supports an approach for pharmacological remediation of cognitive symptoms through manipulations of PFC DA and NE.[2]

Atomoxetine (Strattera, Eli Lilly & Co, Indianapolis, Ind), a selective NE reuptake inhibitor, produces a widespread increase in brain NE and a secondary and selective increase in extracellular DA concentrations in the PFC[3] owing to the nonselectivity of NE transporters in the PFC for both DA and NE[4,5] and the increased competition between NE and DA at these reuptake sites.

Given these data, we evaluated atomoxetine's cognitive effects in a pilot placebo-controlled clinical trial as an adjunct to ongoing second-generation antipsychotic (SGA) treatment in patients with schizophrenia. Moreover, a functional magnetic resonance imaging (fMRI) investigation was undertaken to assess the neural mechanisms underlying the cognitive effects of atomoxetine.

PATIENTS AND METHODS

Subjects

Subjects were recruited from the outpatient psychiatry departments of several New York area hospitals. All subjects provided written informed consent, and this study was carried out in accordance with the Declaration of Helsinki as adopted and promulgated by the National Institutes of Health. All participants met the *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition* diagnostic criteria for schizophrenia using the Comprehensive Assessment of Symptoms and History structured interview.[6] Potential participants were receiving stable doses of one of the following SGA medications for a minimum period of 4 weeks before entry into the study: risperidone, olanzapine, quetiapine, or aripiprazole and no other psychotropic medications.

Assessments

The Positive and Negative Syndrome Scale (PANSS[7]) was used to assess weekly the severity of positive, negative, and general psychopathology symptoms. Cognitive performance was measured by the Brief Assessment of Cognition

in Schizophrenia (BACS[8]). The BACS is specifically designed to measure treatment-related improvements in the domains of reasoning and problem solving, verbal fluency, attention, verbal memory, working memory, and motor speed. A full description of the BACS and its administration has been previously published.[8] A composite score for performance on the BACS was calculated by standardizing the subjects' performance on each measure to the performance of healthy comparison subjects and then calculating the composite from the individual *z* scores.[8]

The Specific Level of Function scale (SLOF[9]), which is a 43-item instrument, rated on a 5-point Likert-type scale, was used to assess functional status in 5 domains measuring living skills and behavior problems. Ratings were generated after related information was obtained from the subject and a corroborative source.

N-Back Task

During the fMRI examination, subjects were shown sequences of letters presented singly in the middle of a visual display mounted in the MRI scanner bore and were asked to provide button presses in response to target stimuli. Working memory load was varied parametrically among 0, 2, and 3 items. In the 0-back condition, the target was the prespecified letter "X". In the 2- and 3-back conditions, the target was a repeated "X" that was presented 2 and 3 trials preceding it, respectively.

TABLE 1. Comparisons of Treatment Groups on Baseline Demographic and Assessment Data

	t test Comparisons of Baseline Values			
	Baseline			
Variable	Placebo Mean (SD)	Atomoxetine Mean (SD)	*t*	*P*
PANSS positive	15.1 (4.5)	13.0 (4.5)	1.04	0.31
PANSS negative	19.3 (5.9)	17.8 (4.8)	0.63	0.54
PANSS general	35.7 (7.5)	30.9 (7.0)	1.49	0.15
BACS standardized *z* scores				
Composite score	−1.22 (0.66)	−1.13 (0.61)	−0.32	0.75
List learning test total	−1.12 (1.31)	−1.38 (0.75)	0.54	0.59
Digit sequencing task	−1.78 (0.89)	−1.02 (1.24)	−1.57	0.13
Token motor task	−1.29 (1.05)	−1.60 (0.94)	0.69	0.50
Category instances test	−0.44 (0.28)	−0.38 (.33)	−0.45	0.66
Controlled oral word association test	−1.02 (0.90)	−0.46 (1.06)	−1.36	0.19
Tower of London test	−1.09 (1.39)	−1.56 (1.46)	0.73	0.48
Symbol coding	−1.97 (1.26)	−2.15 (1.10)	0.35	0.73
SLOF functional domains				
Physical functioning	25.0 (0)	22.9 (3.5)	1.93	0.07
Personal care skills	33.8 (2.8)	33.2 (2.9)	0.47	0.64
Interpersonal Relationships	23.8 (4.6)	24.7 (6.4)	−0.36	0.72
Social acceptability	34.2 (1.1)	34.5 (0.8)	−0.67	0.51
Activities	48.8 (6.0)	49.3 (4.9)	−0.20	0.84
Work skills	23.3 (2.3)	21.5 (4.3)	1.16	0.26

Imaging Procedures

The fMRI system used was a 3.0T Siemens Allegra head dedicated machine. The blood oxygen level-dependent (BOLD) imaging was performed using a gradient echoplanar (GE-EPI) sequence using the following protocol: 32 axial slices 3 mm thick and skip = 1 mm, TR = 2 seconds, TE=40 milliseconds, flip angle = 90 degrees, FOV = 23 CM, matrix = 64 × 64. The number of volumes acquired during each N-back session was 220. Statistical Parametric Mapping (SPM) 2 was used for the imaging preprocessing procedures. All BOLD images were realigned to the first volume and then coregistered with the anatomical T2 image. The T2 image was normalized in SPM2 to the Talairach space. The transformation was then applied to the coregistered BOLD images that were then resampled to 2-mm isotropic voxels. Images were then smoothed with an 8-mm isotropic kernel.

Treatment

After baseline assessments and the first fMRI, subjects were randomly assigned in a 1:1 proportion to receive treatment with 40 mg of atomoxetine or placebo daily during a double-blind parallel-designed 4-week treatment period, following which the dose of atomoxetine was increased to 40 mg twice day (or matching placebo), for an additional 4 weeks. The cognitive, functional, and symptom assessment battery was performed at baseline and weeks 4 and 8, and the fMRI was performed at baseline and week 8.

Analyses

The comparative efficacy of atomoxetine versus placebo on behavioral measures was analyzed with analysis of covariance using the last observation carried forward imputation procedure to examine the interaction between treatment (placebo, atomoxetine) × time (baseline, week 8) on PANSS, BACS, and SLOF measures; the covariate was baseline performance.

Imaging data were analyzed for patient specific N-back related activation under higher working memory loads by pooling the 2- and 3-back conditions and subtracting activation under the 0-back condition. The analysis of treatment effect used *t* tests to compare the difference of differences in baseline versus week 8 comparisons under atomoxetine and placebo conditions. Statistical Parametric Mapping *t* tests were used to identify regions with significant differences thresholded to $P < 0.01$ at the voxel level and thresholded to clusters greater than 40 voxels.

RESULTS

Twenty subjects completed baseline assessments and were randomized to study drug (10 placebo, 10 atomoxetine). Eight subjects in the placebo arm and 7 subjects in the atomoxetine arm completed 8 weeks of treatment. Two subjects in the placebo group terminated at weeks 5 and 6, respectively, due to withdrawal of consent. One subject in the atomoxetine group terminated in week 5 due to a sustained elevation of supine blood pressure from a baseline of 120/76 to 152/92 mm Hg and an increase in pulse from 72 to 87 bpm. Another atomoxetine-treated subject discontinued at week 6 due to urinary hesitancy, and the third subject discontinued

at week 1 due to withdrawal of consent. No significant differences in baseline symptom and cognitive and functional data between treatment groups were observed and are reported in Table 1. Results of the last observation carried forward and observed cases analyses were approximately the same and are presented in Table 2. No significant improvement with atomoxetine compared with placebo was observed for the BACS composite score (0.24 ± 0.31 vs 0.15 ± 0.31, $F_{1,17} = 0.33$, $P = 0.57$). No other significant differences were observed on any of the exploratory measures except for a significantly greater improvement on the Work Skills domain of the SLOF with atomoxetine treatment versus placebo (3.1 ± 3.3 vs 0.3 ± 1.1, $F_{1,17} = 4.69$, $P = 0.04$). This change was not accounted for by a few outliers because 50% of the atomoxetine-treated group demonstrated an improvement on SLOF Work Skills ≥3 points compared with 0% of the placebo group demonstrating this magnitude of improvement. Moreover, changes in item 40 of the SLOF, which assesses ability to sustain work effort without being easily distracted, accounted for 75% of the variance in change scores of the Work Skills subsection of the SLOF. Analysis of the safety data demonstrated a significant increase in supine pulse rate with atomextine treatment compared with placebo (6.9 ± 11.2 mm Hg vs −4.7 ± 11.0 mm Hg, $F_{1,17} = 6.31$, $P = 0.02$). There were no significant differences in blood pressure or any differences in the frequencies of other adverse events between atomoxetine and placebo.

Analyzable fMRI data from both pretreatment and posttreatment scans were available for 8 subjects, 5 from the atomoxetine group and 3 subjects from the placebo group. Statistical Parametric Mapping analysis of fMRI data demonstrated significantly greater posttreatment activation in the left dorsolateral PFC and the left posterior cingulate cortex with atomoxetine compared with placebo under increased working memory load (2- and 3-back minus 0-back) (Fig. 1).

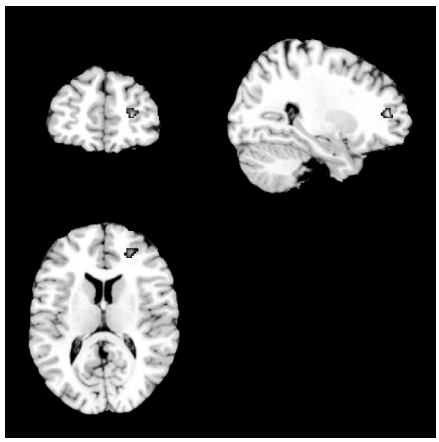
DISCUSSION

We found no significant improvements in any cognitive outcome measures suggestive of a cognitive enhancing effect of atomoxetine. Given that no cognitive enhancing effect was observed with atomoxetine treatment, we were surprised to observe significantly greater increases in working memory-related activation of the left dorsolateral PFC in patients treated with atomoxetine. Equally unexpected in the context of no cognitive enhancing effect was an atomoxetine-related improvement in the functional domain of work skills.

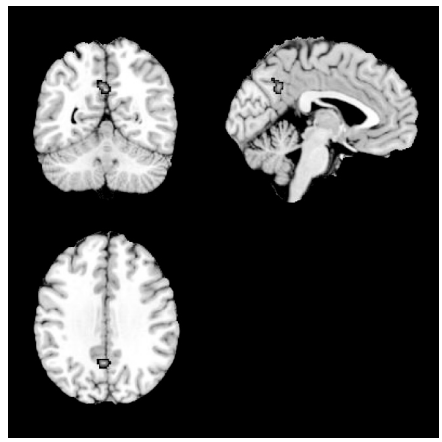
Although the current sample size is small, there were minimal effect sizes detected for changes in performance across the cognitive domains. For instance, the composite score improved by 0.02 SD greater in the active treatment group than the placebo group. This difference is clearly a

TABLE 2. Results of Last Observation Carried Forward and Observed Cases Analyses on Change Scores (Baseline to Week 8) for Symptom, Cognitive and Functional Measures

	Change Scores (Baseline −> Week 8) Last Observation Carried Forward				Change Scores (Baseline −> Week 8) Observed Cases				
Variable	**Placebo (n = 10) Mean (SD)**	**Atomoxetine (n = 10) Mean (SD)**	**F Statistic**	***P***	**Placebo (n = 8) Mean (SD)**	**Atomoxetine (n = 7) Mean (SD)**	**F Statistic**	***P***	**Effect Size**
PANSS positive	−0.5 (4.0)	0.2 (2.9)	0.13	0.72	−0.62 (4.5)	0.9 (3.1)	0.75	0.40	0.34
PANSS negative	−3.8 (5.1)	−1.8 (2.7)	0.74	0.40	−3.8 (5.7)	−2.6 (2.9)	0.02	0.90	0.21
PANSS general	−3.7 (8.0)	−4.2 (4.4)	0.31	0.58	−4.4 (8.9)	−4.7 (5.1)	0.25	0.63	−0.05
BACS standardized *z* scores									
Composite score	0.15 (0.32)	0.24 (0.31)	0.33	0.57	0.26 (0.26)	0.27 (0.34)	0	1.00	0.02
List learning test total	0.45 (1.05)	0.64 (0.89)	0.19	0.67	0.62 (1.02)	0.84 (1.00)	0.16	0.69	0.19
Digit sequencing task	0.13 (0.71)	0.03 (0.84)	0.06	0.80	0.17 (0.78)	0.11 (1.00)	0.81	0.38	−0.05
Token motor task	0.52 (0.86)	0.37 (0.70)	0.68	0.42	0.79 (0.66)	0.46 (0.80)	0.97	0.34	−0.39
Category instances test	0.20 (0.33)	0.13 (0.36)	0.21	0.65	0.22 (0.35)	0.14 (0.31)	0.25	0.63	−0.27
Controlled oral word association test	0.01 (0.86)	−0.01 (0.68)	0.01	0.93	0.07 (0.47)	0.24 (0.64)	0.19	0.67	0.16
Tower of London test	−0.30 (1.38)	0.41 (0.65)	1.54	0.23	0.02 (0.87)	0.31 (0.64)	0.47	0.51	0.24
Symbol coding	0.20 (0.79)	0.33 (0.68)	0.09	0.77	0.39 (0.63)	0.28 (0.79)	0.03	0.88	−0.09
SLOF functional domains									
Physical functioning	−0.2 (0.4)	0.4 (1.2)	0.02	0.90	−0.3 (0.5)	0 (1.0)	0.30	0.60	0
Personal care skills	0.3 (1.4)	0.3 (1.0)	0.55	0.47	0.4 (1.5)	0.6 (0.9)	0.06	0.81	0.06
Interpersonal relationships	1.6 (3.4)	2.5 (3.9)	0.79	0.39	1.9 (3.7)	3.1 (4.5)	1.60	0.23	0.24
Social acceptability	0.1 (0.9)	−0.1 (0.6)	0.12	0.74	0.1 (1.0)	0 (0.6)	0.01	0.94	0
Activities	0.6 (2.9)	0.7 (2.7)	0.03	0.87	0.6 (3.2)	0.6 (3.3)	0.01	0.91	0
Work skills	0.3 (1.1)	3.1 (3.3)	4.69	0.04	−0.1 (0.6)	2.9 (3.3)	5.50	0.03	0.81



Left Dorsolateral Prefrontal Cortex



Left Posterior Cingulate Cortex

SPM Results

Region of Interest	Coordinates In Standard Stereotactic Space			Cluster Level	Voxel Level		
	X	*Y*	*Z*	K_E	*T*	Z_E	$P_{uncorrected}$
Left Dorsolateral Prefrontal Cortex	–28	–46	10	43	7.38	3.60	< 0.001
Left Posterior Cingulate Cortex	–2	–56	32	66	6.98	3.52	< 0.001

FIGURE 1. Areas of significantly greater working memory-related activation produced by atomoxetine treatment overlaid on T1 high-resolution images.

very small effect size and would only be statistically significant in a very substantial sample, whereas the clinical meaningfulness of such a small differential change would likely be minimal.

The negative results of the current study contrast the demonstrated ability of amphetamine to improve executive cognitive functions of schizophrenic patients.[10] We reasoned that the combined DA and NE increases in the PFC produced by atomoxetine,[3] similar to psychostimulants, would address some of the schizophrenia-related neurochemical changes in the PFC thought to contribute to the cognitive impairment of schizophrenia.[2] Although the results of the current study showed atomoxetine to produce significant working memory-related activation of the left dorsolateral PFC similar to amphetamine,[10] it did not produce activation of occipital and anterior cingulate cortices seen with amphetamine.[10] Moreover, amphetamine produces deactivation elsewhere in the cortex and subcortex,[10,11] which we did not observe with atomoxetine. Indeed, the normal pattern of brain activation during working memory performance shows a complex pattern of activated areas in prefrontal, premotor, and anterior cingulate cortices synchronized to a system of deactivated regions in temporal, posterior cingulate, parieto-occipito cortices, and striatum.[12] In contrast to the normal pattern of deactivation, we found atomoxetine in the present study to increase posterior cingulate activation during working memory task performance. Moreover, patients with schizophrenia show both task-related reduced activation in the dorsolateral prefrontal, anterior cingulate, and parietal cortices and reduced deactivation in temporal and posterior cingulate regions compared with healthy volunteers.[12,13] Given these data, the results of the present study suggest that atomoxetine may have aggravated the impaired deactivation of the posterior cingulate observed in schizophrenic patients performing cognitive tasks.[12,13] Therefore, the effects of atomoxetine in the posterior cingulate cortex may have countered its beneficial effects in the dorsolateral PFC.

Another potential reason for the inability of atomoxetine to improve cognition in the present study is related to the extent which atomoxetine may increase PFC activation in the face of treatment with SGAs. For example, a switch from first-generation antipsychotic treatment to risperidone has been associated with enhanced activation of the PFC during working memory performance in patients with schizophrenia.[14] Therefore, the addition of atomoxetine to ongoing SGA treatment in the present study may have produced excessive prefrontal activation above levels optimal for working memory performance.[15]

The improvement in the functional domain of work skills associated with atomoxetine treatment is intriguing, yet problematic. This pilot study was not sufficiently powered for these findings to have survived Bonferoni correction; therefore, one cannot exclude the possibility of this being a chance finding. Findings such as these occur frequently in small pilot studies, and no conclusions should be drawn from this. However, given the present lack of viable treatments to significantly enhance the functional capacity of schizophrenic patients, these findings may warrant further investigation, perhaps with performance-based measures of functional capacity.

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