# A Randomized Double-Blind Trial of Atomoxetine for Cognitive Impairments in 32 People With Schizophrenia

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***Background:*** Currently available antipsychotic medications offer only modest, if any, effects on cognitive performance in people with schizophrenia. Treatments that would improve these impairments could lead to better functional outcomes. Atomoxetine is a nonstimulant, selective norepinephrine reuptake inhibitor approved for the treatment of attention-deficit/hyperactivity disorder. In animals, it has been shown to increase extracellular levels of acetylcholine and dopamine in cortical and hippocampal regions.

***Method:*** Following a 2-week stabilization period, 32 subjects with DSM-IV–diagnosed schizophrenia or schizoaffective disorder were randomly assigned to atomoxetine (80 mg daily) or placebo for 8 weeks. All subjects were treated with antipsychotic monotherapy (excluding clozapine, aripiprazole, and first-generation antipsychotics). Neuropsychological test performance was the primary outcome variable, and the neuropsychological test battery included measures of attention, motor speed, executive function, processing speed, verbal and visual memory, and working memory (rated at baseline and end point). Symptom and side-effect ratings were performed every 2 weeks. The study was conducted from April 2004 through December 2006.

***Results:*** There were no treatment group differences on the primary study outcome measure (overall mean z-score: Wilcoxon $\chi^2 = 0.21$, df = 1, p = .64); nor was there significant evidence of variation in treatment effects on z-score changes across the individual neuropsychological tests ($\chi^2 = 8.22$, df = 8, p = .41). No between-group differences were noted in symptom changes. Atomoxetine was well tolerated and was associated with a trend for improvement in extrapyramidal side effects relative to placebo (p = .063).

***Conclusion:*** Our results provide further evidence that atomoxetine has limited benefit for improving cognition in people with schizophrenia.

***Trial Registration:*** clinicaltrials.gov Identifier: NCT00161031

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Schizophrenia is characterized by a broad range of cognitive impairments.[1,2] These impairments occur early in the course of the illness, and they are a persistent and core feature of the illness. Most important for treatment development, evidence is emerging that improved cognitive functioning, more so than positive symptom changes, leads to better functional outcomes for people with schizophrenia.[3,4]

Currently available antipsychotic treatments offer only modest, if any, enhancements of cognitive performance,[5–7] which may be explained by repeated testing effects.[6] The lack of available treatment strategies in this domain has led to recent attempts to develop and study new agents for targeting cognition.[8] Targets for adjunctive pharmacologic treatments currently under study include agents that modulate the dopamine $D_1$ receptors in the prefrontal cortex, the serotonin receptors in the prefrontal cortex and anterior cingulate cortex, the glutamatergic excitatory synapse, the acetylcholine nicotinic receptors in the hippocampus, the acetylcholine muscarinic receptors, and the brain γ-aminobutyric acid system.[9,10]

Atomoxetine is 1 potential target for cognitive enhancement in schizophrenia due to its ability to indirectly but selectively increase extracellular dopamine concentrations in the prefrontal cortex.[11] Atomoxetine

is a nonstimulant, selective norepinephrine reuptake inhibitor approved for the treatment of attention-deficit/hyperactivity disorder.[12] In animal models, atomoxetine increases in vivo extracellular levels of acetylcholine in cortical but not subcortical brain regions.[13] Atomoxetine has similar effects on hippocampal acetylcholine release mediated by both norepinephrine $\alpha_1$ and dopamine $D_1$ receptor activation.[13] Additionally, atomoxetine causes cortical dopamine and norepinephrine release, which does not appear to occur in the striatum or nucleus accumbens, and has been found to significantly improve memory functions in rodents.[13,14]

In a single-dose study[15] in adults with attention-deficit/hyperactivity disorder, atomoxetine treatment improved response inhibition, and in a clinical trial,[16] atomoxetine was also found to reduce executive function deficits. Similarly, in a study[17] in children with attention-deficit/hyperactivity disorder, the authors found reduced attention deficits as early as 1 week after the initiation of treatment. Recently, a small double-blind pilot study[18] reported no significant global improvements in cognition with atomoxetine compared to placebo in people with schizophrenia. However, they did find significantly greater increases in working memory–related activation of the left dorsolateral prefrontal cortex in patients treated with atomoxetine.[18]

In this pilot study, conducted from April 2004 through December 2006, we examined the effects of adjunctive atomoxetine on cognitive functioning in 32 subjects with schizophrenia in a double-blind, 8-week, placebo-controlled study.

## METHOD

### Subject Characteristics

All participants in this study met DSM-IV diagnostic criteria for schizophrenia or schizoaffective disorder using the Structured Clinical Interview for DSM-IV.[19] Additionally, participants met a priori criteria for cognitive impairment. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[20] was used to determine the level of cognitive impairment. Participants were required to have a score of 90 or less on the RBANS, a score that is two thirds of a standard deviation below the normal standardization sample mean of 100. All participants were required to be treated and stabilized on a second-generation antipsychotic regimen, excluding clozapine and aripiprazole, and continued on an unchanged dose for at least 4 weeks prior to randomization. Inpatients and outpatients between the ages of 18 and 60 years were included. Participants with a history of organic brain disease, DSM-IV diagnosis of alcohol or substance abuse within the last month or dependence within the last 6 months, current pregnancy, uncontrolled hypertension (blood pressure exceeding 140/90 mm Hg on 3 consecutive readings despite adequate treatment), or the concurrent use of venlafaxine or monoamine oxidase inhibitors were excluded from the study. Anticholinergic medications and benzodiazepines were excluded except for p.r.n. doses of benztropine and lorazepam for anxiety, agitation, or akathisia. Participants also were required to be on a stable dose of all other psychotropic medications including antidepressants and mood stabilizers for at least 4 weeks prior to random assignment. No medication changes or changes in dose of existing medications were permitted during the study period.

The University of Maryland School of Medicine Institutional Review Board approved the study protocol and informed-consent procedures. Written informed consent was obtained for all participants after the study procedures had been fully explained and before study participation. The ability of each subject to provide valid informed consent was documented by using study-specific procedures.

### Study Design

This 8-week, randomized, double-blind trial examined the effects of adjunctive atomoxetine treatment in people with schizophrenia or schizoaffective disorder who have moderate to high levels of cognitive impairment. After a 2-week stabilization period, participants were randomly assigned to atomoxetine or placebo. In the 2-week stabilization phase, participants underwent baseline symptom, medical, safety, and neuropsychological assessments.

### Dosing and Titration

In the first 2 weeks of randomization, subjects were initiated on atomoxetine 40 mg/day or matching placebo given once daily. At week 3, participants were titrated to 80 mg/day (given as two 40-mg capsules), administered once daily, and continued on that dose for the remaining 6 weeks. Subjects randomly assigned to placebo were given an equal number of matched placebo capsules.

### Neuropsychological Assessments

Neuropsychological testing occurred at baseline and at 8 weeks (end point). The neuropsychological test battery consisted of the following measures: working memory: Wechsler Adult Intelligence Scale-III (WAIS-III) Letter-Number Sequencing[21] and Number Sequencing Test[22]; processing speed: WAIS-III Digit Symbol[21]; motor speed: Grooved Pegboard[23]; verbal fluency: Letter Fluency[24]; problem solving: Woodcock Johnson Planning[25]; verbal learning: California Verbal Learning Test[26]; visual memory: Brief Visuospatial Memory Test[27]; and attention: distractibility version of the Gordon Diagnostic System (GDS) Continuous Performance Test.[28]

### Clinical Assessments

Symptoms were evaluated at baseline and every 2 weeks during the double-blind phase with the Brief

Psychiatric Rating Scale (BPRS),[29] a modified form of the Scale for the Assessment of Negative Symptoms (SANS)[30,31] adapted for use with both inpatients and outpatients, and the Clinical Global Impressions Scale (CGI).[32] The BPRS positive symptom items (conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content[33,34]) were used to assess positive symptoms, and the BPRS anxiety/depression (somatic concern, anxiety, guilt feelings, and depression items) and hostility (hostility and uncooperativeness) factors[29] were used to assess changes in those symptom domains. Change in negative symptoms was assessed using a modified SANS total score that included all items except global items, inappropriate affect, poverty of content of speech, social inattentiveness, and inattentiveness during mental status testing.[33] The CGI Severity of Illness[32] score assessed global changes in clinical state.

### Safety Assessments

Safety assessments included the Simpson-Angus Scale,[35] the Abnormal Involuntary Movement Scale (AIMS),[36] the Barnes Akathisia Scale,[37] and a Side Effect Checklist (R.W.B., unpublished checklist, 1991). These assessments were performed every 2 weeks. Participants were considered to have akathisia present with a Barnes Akathisia Scale global rating of $\geq 2$. Changes in total body weight, body mass index, pulse, and blood pressure were also evaluated every 2 weeks. Electrocardiogram, fasting lipid profile, and fasting serum glucose were evaluated at baseline and end point.

### Concomitant Medications

Participants were permitted to take, as needed, benztropine (1–6 mg/day) for extrapyramidal symptoms, lorazepam (1–6 mg/day) for anxiety, agitation, or akathisia, and chloral hydrate (500–1000 mg/day) for sleep. To minimize the effects of the p.r.n. medications on test results, participants were not to receive any of the above p.r.n. medications 12 hours prior to neuropsychological testing. Additionally, participants requesting the use of benztropine or any antiparkinsonian agent were first assessed with a movement rating scale to document the presence of extrapyramidal symptoms prior to receiving the antiparkinsonian treatments and were not permitted to have received any antiparkinsonian agent within 12 hours prior to the movement assessment.

### Statistical Analysis

For each neuropsychological test, subject scores were converted to z-scores: z = (score – baseline mean)/baseline SD. For the primary outcome measure, an overall composite z-score was computed from the mean of the individual test z-scores. Preliminary data inspection suggested that, even after transformation to z-scores, many of the test scores were not normally distributed, and, accordingly, the Wilcoxon rank sum test was used to compare treatments. An adaptation of the Pepe method[38] was used to test for heterogeneity of effect across neuropsychological tests. In brief, the generalized estimating equations method for unbalanced repeated-measures analysis of variance was used to fit the model change in z-score = treatment + tests + treatment $\times$ test to the individual test z-scores; a significant treatment $\times$ test interaction score indicates heterogeneity of effect sizes among the different tests. Post hoc analyses of individual neuropsychological test treatment differences were performed, with p values adjusted for multiple comparisons using the Benjamini and Hochberg[39] procedure to control the false discovery rate.

Mixed-model analysis of covariance was used to examine changes in symptoms, blood pressure, vital signs, lipids, and continuous electrocardiogram measures. Longitudinal trends in repeated Simpson-Angus Scale and AIMS assessments were compared using the following procedure: for each subject, the Kendall $\tau$-b rank correlation was calculated between outcome and visit, and the distribution of these correlations was compared using the Conover-Salsburg rank test.[40] This procedure has superior power to mixed models for repeated-measures analysis of variance for outcomes with nonnormal distributions, in which only a subgroup of participants may "respond" to treatment.[41] For Side Effect Checklist items, treatments were compared using the Fisher exact test on presence or absence of newly incident or worsened (compared to baseline) side effects.

## RESULTS

Forty-four participants were screened for inclusion in the study, 34 participants entered the 2-week evaluation phase, and 32 participants were randomly assigned (16 each to atomoxetine and placebo). In the atomoxetine group, 3 participants discontinued: 1 was nonadherent, 1 was lost to follow-up, and 1 dropped out due to lack of concentration and feeling strange. In the placebo group, 4 participants were discontinued: 1 was nonadherent, 1 was lost to follow-up, and 2 were withdrawn for worsening of psychotic symptoms. Two subjects in the atomoxetine group were excluded from analysis due to treatment with aripiprazole, an antipsychotic with partial $D_2$ agonist activity in the prefrontal cortex and a potential confound to the question under study. Thus, there were 14 participants included for atomoxetine and 16 for placebo.

### Demographic Information

Table 1 lists baseline demographic information. During the study, 5 participants receiving atomoxetine and 8 participants receiving placebo were also receiving olanzapine, 1 in each group was receiving quetiapine, and 5 receiving atomoxetine and 6 receiving placebo were also

**Table 1. Demographic Characteristics of People Who Received Atomoxetine or Placebo for Cognitive Impairments**

| Characteristic | (N = 10) Atomoxetine | (N = 12) Placebo | Statistics Test | df | p Value |
|---|---|---|---|---|---|
| Age, mean ± SD, y | 48.9 ± 5.7 | 49.1 ± 8.5 | Wilcoxon $\chi^2 = 0.00$ | 1 | .99 |
| Sex, male, n/N (%) | 8/10 (80) | 8/12 (67) | Fisher exact test | | .65 |
| Race, n/N (%) | | | Fisher exact test | | .65 |
| White | 4/10 (40) | 7/12 (58) | | | |
| African American | 6/10 (60) | 5/12 (42) | | | |
| Age at first psychiatric hospitalization, mean ± SD, y | 26.1 ± 9.7 | 24.5 ± 5.5 | Wilcoxon $\chi^2 = 0.03$ | 1 | .86 |
| RBANS score, mean ± SD | 70.2 ± 10.3 | 66.1 ± 10.9 | Wilcoxon $\chi^2 = 1.25$ | 1 | .26 |

Abbreviation: RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

**Table 2. Neuropsychological Test Scores of People With Schizophrenia Who Received Atomoxetine or Placebo Over 8 Weeks for Cognitive Impairments**

| Test and Time Point | Atomoxetine (N = 10), Mean ± SD | Placebo (N = 12), Mean ± SD | Effect Size | Wilcoxon Test for Between-Group Difference in Change Score[a] $\chi^2$ (df = 1) | Unadjusted p Value | Adjusted p Value |
|---|---|---|---|---|---|---|
| Overall mean z-score | | | 0.14 | 0.21 | .644 | .974 |
| Baseline | 0.14 ± 0.52 | –0.13 ± 0.72 | | | | |
| End point | 0.26 ± 0.47 | –0.09 ± 0.56 | | | | |
| Change in z-score | 0.13 ± 0.38 | 0.04 ± 0.29 | | | | |
| WAIS-III Letter-Number Sequencing score | | | | 0.09 | .764 | .974 |
| Baseline | 0.20 ± 0.67 | –0.16 ± 1.20 | –0.04 | | | |
| End point | 0.35 ± 0.97 | 0.03 ± 0.76 | | | | |
| Change in z-score | 0.15 ± 0.54 | 0.19 ± 0.94 | | | | |
| WAIS-III Digit Symbol score | | | | 0.26 | .607 | .974 |
| Baseline | 0.31 ± 1.07 | –0.26 ± 0.90 | –0.14 | | | |
| End point | 0.31 ± 0.91 | –0.12 ± 0.95 | | | | |
| Change in z-score | 0.00 ± 0.73 | 0.13 ± 0.55 | | | | |
| Grooved Pegboard score[b] | | | | 0.50 | .477 | .974 |
| Baseline | –0.28 ± 0.94 | 0.21 ± 1.03 | 0.01 | | | |
| End point | –0.33 ± 0.75 | 0.16 ± 1.53 | | | | |
| Change in z-score | –0.04 ± 0.45 | –0.05 ± 0.67 | | | | |
| Letter Fluency score[c] | | | | 0.06 | .805 | .974 |
| Baseline | 0.07 ± 0.90 | 0.06 ± 1.08 | 0.27 | | | |
| End point | 0.37 ± 1.36 | 0.08 ± 1.10 | | | | |
| Change in z-score | 0.30 ± 0.95 | 0.03 ± 0.71 | | | | |
| Woodcock-Johnson Planning Test score[d] | | | | 0.01 | .938 | .974 |
| Baseline | 0.43 ± 0.92 | –0.29 ± 0.98 | 0.20 | | | |
| End point | 0.58 ± 0.63 | –0.34 ± 0.75 | | | | |
| Change in z-score | 0.15 ± 0.89 | –0.05 ± 0.66 | | | | |
| California Verbal Learning Test score | | | | 3.93 | .047 | .474 |
| Baseline | 0.11 ± 0.91 | –0.10 ± 1.10 | 0.45 | | | |
| End point | 0.31 ± 0.86 | –0.36 ± 1.31 | | | | |
| Change in z-score | 0.20 ± 0.25 | –0.26 ± 0.82 | | | | |
| Brief Visuospatial Memory Test score | | | | < 0.01 | .974 | .974 |
| Baseline | 0.29 ± 1.07 | –0.24 ± 0.92 | –0.09 | | | |
| End point | 0.36 ± 1.08 | –0.08 ± 0.94 | | | | |
| Change in z-score | 0.07 ± 1.01 | 0.16 ± 0.54 | | | | |
| GDS Distractibility Test score[e] | | | | 0.24 | .622 | .974 |
| Baseline | 0.20 ± 0.58 | –0.18 ± 1.27 | 0.23 | | | |
| End point | 0.50 ± 0.52 | –0.12 ± 1.14 | | | | |
| Change in z-score | 0.30 ± 0.42 | 0.06 ± 0.76 | | | | |
| Number Sequencing score | | | | 0.19 | .664 | .974 |
| Baseline | 0.10 ± 1.04 | –0.08 ± 1.00 | –0.14 | | | |
| End point | 0.18 ± 0.83 | 0.14 ± 0.93 | | | | |
| Change in z-score | 0.08 ± 0.82 | 0.22 ± 0.74 | | | | |

[a]Test for heterogeneity of z-score differences between treatments among neuropsychological outcomes: $\chi^2 = 8.22$, df = 8, p = .41. Wilcoxon tests were used to evaluate treatment differences in neuropsychological changes from baseline to end of study. The Benjamini and Hochberg[39] multiple test procedure was used to control the false discovery rate during multiple testing and to calculate adjusted p values.
[b]For Grooved Pegboard score, atomoxetine N = 9.
[c]For Letter Fluency score, placebo N = 11.
[d]For Woodcock-Johnson Planning Test, atomoxetine N = 8.
[e]For GDS Distractibility Test, placebo N = 11.
Abbreviations: GDS = Gordon Diagnostic System, WAIS-III = Wechsler Adult Intelligence Scale-III.

receiving risperidone. There were no differences in proportion of atomoxetine and placebo participants taking mood stabilizers (1 vs. 4, respectively), antidepressants (6 vs. 6, respectively), p.r.n. benzodiazepines (1 vs. 2, respectively), and p.r.n. anticholinergic medications (0 vs. 2, respectively).

### Neuropsychological Assessments

Table 2 lists baseline, end-point, and change scores for all neuropsychological tests. There were no treatment group differences on the primary study outcome measure (overall mean z-score: Wilcoxon $\chi^2 = 0.21$, df = 1, p = .64); nor was there significant evidence of variation in treatment effects on z-score changes across the individual neuropsychological tests ($\chi^2 = 8.22$, df = 8, p = .41). Exploratory analyses of individual neuropsychological tests showed a performance advantage on the California Verbal Learning Test in participants treated with adjunctive atomoxetine compared to placebo (unadjusted p value: p = .047; p value adjusted for multiple testing: p = .474). The effect size of the difference in mean California Verbal Learning Test scores was considered moderate (0.45). However, this result was influenced by an unexpected decline in performance on the task in the placebo group, as well as by improvement in the treatment group. Other neuropsychological tests did not differ between treatment arms (minimum unadjusted p value: p = .48).

### Clinical Assessments

Table 3 displays baseline and end-point BPRS total score, BPRS positive symptom item score, BPRS anxiety/depression and hostility factor scores, SANS total score, and CGI score. There were no significant main effects of treatment or treatment-by-time interactions for any symptom domain.

### Side Effect Ratings

Mean ± SD Simpson-Angus Scale scores in the atomoxetine group at baseline and end point were 2.0 ± 3.6 and 0.4 ± 0.5, respectively, and in the placebo group, the baseline and end-point means were 2.1 ± 1.9 and 1.9 ± 2.6, respectively (Conover-Salsburg rank test: F = 3.81, df = 1,24; p = .063). The mean ± SD AIMS total scores at baseline and end point were 2.5 ± 3.5 and 2.5 ± 3.4, respectively, in the atomoxetine group and 2.6 ± 3.6 and 2.3 ± 2.9, respectively, in the placebo group (Conover-Salsburg rank test: F = 1.17, df = 1,24; p = .29). No participants in the atomoxetine group were characterized as having akathisia present at baseline or at end point. One atomoxetine subject was rated as having akathisia at week 4; however, this was resolved by study conclusion. In the placebo group, 1 subject had akathisia at baseline, and 3 reported akathisia at end point (p = .614, Fisher exact test). Tables 4 and 5 list side effects and laboratory changes, respectively. There were no significant group differences in any of the laboratory or side-effect measures.

**Table 3. Clinical Symptom Ratings for People With Schizophrenia Who Received Atomoxetine or Placebo for Cognitive Impairments**

| Scale and Time Point | Atomoxetine,[a] Mean ± SD | Placebo,[b] Mean ± SD | Statistics F | df | p Value |
|---|---|---|---|---|---|
| BPRS total score | | | 0.57 | 1,22 | .458 |
| Baseline | 32.5 ± 9.7 | 39.8 ± 9.9 | | | |
| End point | 30.2 ± 8.2 | 36.0 ± 11.6 | | | |
| BPRS positive symptom score | | | 0.00 | 1,22 | .989 |
| Baseline | 10.0 ± 5.0 | 12.1 ± 5.1 | | | |
| End point | 9.8 ± 4.9 | 10.3 ± 5.5 | | | |
| BPRS anxiety/depression score | | | 0.10 | 1,23 | .754 |
| Baseline | 6.6 ± 3.3 | 8.7 ± 4.2 | | | |
| End point | 6.4 ± 1.9 | 8.3 ± 3.6 | | | |
| BPRS hostility score | | | 0.03 | 1,22 | .874 |
| Baseline | 5.3 ± 2.5 | 6.9 ± 2.8 | | | |
| End point | 4.5 ± 1.8 | 5.5 ± 3.0 | | | |
| SANS total score | | | 0.59 | 1,23 | .450 |
| Baseline | 34.1 ± 19.8 | 36.8 ± 13.9 | | | |
| End point | 32.5 ± 16.1 | 38.2 ± 13.8 | | | |
| CGI score | | | 0.22 | 1,24 | .644 |
| Baseline | 4.3 ± 0.9 | 4.7 ± 0.7 | | | |
| End point | 4.2 ± 0.9 | 4.8 ± 0.8 | | | |

[a]Baseline N = 11; end point N = 11.
[b]Baseline N = 15; end point N = 12.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions Scale, SANS = Scale for the Assessment of Negative Symptoms.

**Table 4. Side Effects Reported in People With Schizophrenia Who Received Atomoxetine or Placebo for Cognitive Impairments**

| Side Effect | Atomoxetine (N = 11), N (%) | Placebo (N = 15), N (%) | Statistics F | p Value |
|---|---|---|---|---|
| Nausea | 0 | 4 (27) | 11 | .113 |
| Vomiting | 0 | 2 (13) | 11 | .492 |
| Diarrhea | 0 | 2 (13) | 11 | .492 |
| Anorexia (loss of appetite) | 0 | 3 (20) | 11 | .239 |
| Weight loss | 1 (9) | 3 (20) | 10 | .614 |
| Insomnia | 2 (18) | 1 (7) | 9 | .556 |
| Abdominal pain | 2 (18) | 2 (13) | 9 | 1.000 |
| Tremor | 2 (18) | 3 (20) | 9 | 1.000 |
| Stiffness | 1 (9) | 5 (33) | 10 | .197 |
| Restlessness | 3 (27) | 3 (20) | 8 | 1.000 |
| Sore throat | 0 | 2 (13) | 11 | .492 |
| Dry mouth | 4 (36) | 1 (7) | 7 | .128 |
| Constipation | 1 (9) | 3 (20) | 10 | .614 |
| Sedation | 1 (9) | 2 (13) | 10 | 1.000 |
| Malaise (weakness, fatigue) | 2 (18) | 1 (7) | 9 | .556 |
| Dizziness | 1 (9) | 1 (7) | 10 | 1.000 |

## DISCUSSION

The results of this pilot study suggest that the addition of atomoxetine to antipsychotic treatment does not

**Table 5. Laboratory Measures of People With Schizophrenia Who Received Atomoxetine or Placebo for Cognitive Impairments**

| Variable | Atomoxetine (N = 11), Mean ± SD | Placebo (N = 12), Mean ± SD | Statistics[a] | | |
|---|---|---|---|---|---|
| | | | F or $\chi^2$ | df | p Value |
| Weight, lb | | | F = 1.12 | 1,22 | .301 |
| Baseline | 221.8 ± 35.8 | 222.0 ± 46.9[b] | | | |
| End point | 223.7 ± 35.7 | 222.1 ± 47.9 | | | |
| Body mass index, kg/m$^2$ | | | F = 1.44 | 1,22 | .242 |
| Baseline | 33.8 ± 7.8 | 33.6 ± 6.6[b] | | | |
| End point | 34.1 ± 7.9 | 34.1 ± 6.8 | | | |
| Total cholesterol, mg/dL | | | $\chi^2$ = 1.64 | 1 | .200 |
| Baseline | 188.4 ± 33.4 | 194.2 ± 27.9 | | | |
| End point | 187.8 ± 26.1 | 184.1 ± 33.0 | | | |
| High-density lipoprotein cholesterol, mg/dL | | | $\chi^2$ = 0.37 | 1 | .545 |
| Baseline | 47.4 ± 12.2 | 45.3 ± 8.0 | | | |
| End point | 45.5 ± 11.3 | 45.0 ± 8.9 | | | |
| Low-density lipoprotein cholesterol, mg/dL | | | $\chi^2$ = 1.39 | 1 | .239 |
| Baseline | 112.5 ± 32.9 | 113.8 ± 23.9 | | | |
| End point | 111.3 ± 22.6 | 99.6 ± 28.7 | | | |
| Triglycerides, mg/dL | | | $\chi^2$ = 0.32 | 1 | .570 |
| Baseline | 142.5 ± 64.3 | 175.2 ± 86.0 | | | |
| End point | 155.8 ± 53.5 | 251.5 ± 331.2 | | | |
| Fasting serum glucose, mg/dL | | | $\chi^2$ = 0.34 | 1 | .558 |
| Baseline | 101.6 ± 13.2 | 106.0 ± 23.9 | | | |
| End point | 98.4 ± 27.6 | 107.2 ± 49.8 | | | |
| Heart rate, beats/min | | | F = 1.13[c] | 1,23 | .298 |
| Baseline | 84.3 ± 14.1 | 83.6 ± 11.0[b] | | | |
| End point | 92.8 ± 16.3 | 78.5 ± 7.2 | | | |
| Systolic blood pressure, mm Hg | | | F = 0.00 | 1,23 | .951 |
| Baseline | 126.2 ± 10.3 | 124.8 ± 13.6[b] | | | |
| End point | 131.3 ± 12.5 | 125.2 ± 17.5 | | | |
| Diastolic blood pressure, mm Hg | | | F = 1.15 | 1,22 | .296 |
| Baseline | 78.8 ± 5.9 | 81.3 ± 10.4[b] | | | |
| End point | 83.4 ± 9.4 | 82.3 ± 6.8 | | | |

[a]Mixed-model analysis of covariance was used to examine mean changes between treatment groups in repeated measures of weight, body mass index, heart rate, and blood pressure. Wilcoxon tests were used to compare changes in blood chemistry measures assessed only at end point. Wilcoxon test was used to test the difference in change from baseline between treatment groups in laboratory measures and electrocardiogram.
[b]Baseline N = 15.
[c]Treatment × week was statistically significant in the mixed model: F = 3.23, df = 1, p = .028.

improve global neuropsychological functioning in schizophrenia. Our results also showed no benefit of atomoxetine treatment for performance on individual working memory tasks that might be more specific measures of prefrontal cortical enhancement. Exploratory analyses revealed a small benefit of atomoxetine treatment relative to placebo in verbal learning and memory performance, but only in the unadjusted analyses.

In the only other double-blind study of atomoxetine in schizophrenia reported to date, Friedman and colleagues[18] similarly found no significant improvements in cognitive functioning. Although these investigators reported significant increases in working memory–related activation of the left dorsolateral prefrontal cortex in patients treated with atomoxetine, this activation was accompanied by significant reductions in expected deactivations, specifically in the posterior cingulate. They speculated that the abnormal deactivation may have countered any beneficial effect of increased prefrontal cortex activation.[18] Current results shed no further light on this issue.

The Web site ClinicalTrials.gov lists a number of other ongoing atomoxetine trials in schizophrenia, including several with substantial samples, so there will be more data on this use of atomoxetine for cognitive impairment in schizophrenia. However, these initial studies are not promising.

In our study, atomoxetine was well tolerated. There were no group differences in side effects. Atomoxetine treatment did produce a significant increase in pulse but not a corresponding increase in blood pressure. A trend for significant improvements in extrapyramidal side effects was noted in the atomoxetine group relative to placebo. Interestingly, this finding also parallels a significant finding from our recent galantamine study.[42] While the mechanisms of these effects are unclear, increased dopamine transmission with atomoxetine may play a role.

Despite these largely negative findings, the noradrenergic system remains a potential target for drug development to address cognition in schizophrenia because it may provide a way to enhance catecholamine neurotransmission, but with a lower risk of side effects than with the psychostimulants.[14] Agents that are more selective for $\alpha_2$ noradrenergic receptors may fare better than atomoxetine.[11] At the same time, it is increasingly apparent that there will be no simple pharmacologic answer to the problem of impaired cognitive performance in schizophrenia.

Notwithstanding plausible neurobiologic rationales and positive findings in other conditions, such as Alzheimer's disease and attention-deficit disorder, results in the latest round of rigorous schizophrenia trials have been modest[42] or negative[18,30] on neuropsychological outcome variables—and the field is only just beginning to address more functionally relevant outcomes.[18] While the concerted effort to address cognitive impairment in schizophrenia is still relatively new, this experience should be sobering. Newer agents under development and in initial evaluations may offer enhanced performance by targeting neural systems more precisely,[43] but our optimism should be tempered by results to date.

In conclusion, we were unable to observe an overall effect of atomoxetine treatment on global measures of cognitive function. This is despite having a pharmacologic mechanism of interest for cognitive function, an adequate sample size to detect a difference, and a study design based on consensus standards for studying neurocognitive function.[44] Our results, combined with results from the other published report,[18] do not support the use of adjunctive atomoxetine to improve cognitive performance in schizophrenia.

***Drug names:*** aripiprazole (Abilify), atomoxetine (Strattera), benztropine (Cogentin and others), clozapine (FazaClo, Clozaril, and others), galantamine (Razadyne), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel).

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