Addition of Atomoxetine for Depression Incompletely Responsive to Sertraline: A Randomized, Double-Blind, Placebo-Controlled Study

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Objective: Despite appropriate treatment with selective serotonin reuptake inhibitors (SSRIs), many depressed patients do not attain remission. Addition of a noradrenergic intervention in patients poorly or partially responsive to SSRIs may improve outcomes, but few well-controlled studies testing this hypothesis have been reported.

Method: Patients with major depressive disorder (confirmed by the Structured Clinical Interview for DSM-IV) were treated with sertraline at doses up to 200 mg/day in this study, conducted from June 18, 2003, to January 28, 2005. Patients who continued to experience depressive signs and symptoms after 8 weeks were randomly assigned to have atomoxetine 40 to 120 mg/day or placebo added to sertraline for a further 8 weeks.

Results: Of 276 patients starting the study, 146 with persistent depressive symptoms after 8 weeks of sertraline treatment (mean [SD] final sertraline dose: 161.1 [43.4] mg/day) were randomly assigned to addition of atomoxetine or placebo. After 8 additional weeks, there was no difference between treatment groups in mean change in symptom severity or in the proportion of patients whose symptoms remitted (sertraline/atomoxetine 29/72 [40.3%], sertraline/placebo 28/74 [37.8%], p = .865). Secondary analyses that separated the subgroups with improvements in symptoms that did not reach remission (partial responders) and those with little or no improvement (nonresponders) also showed no effect of atomoxetine. The number of patients discontinuing because of adverse events did not differ between groups.

Conclusion: In depressed patients with persistent symptoms after an initial trial of sertraline, addition of atomoxetine did not improve response more than placebo.

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In recent years, the selective serotonin reuptake inhibitors (SSRIs) have become the most widely prescribed drugs for the treatment of depression. However, even with adequate treatment (time and dose), many depressed patients treated with SSRIs remain symptomatic and require further medical intervention. One potential treatment strategy for such patients is to target a different pharmacologic mechanism, and an obvious candidate intervention is the addition of a norepinephrine reuptake inhibitor. The evidence that some patients have a polymorphism (*s*/*s* allele) in the promoter region of the serotonin transporter gene (*5-HTTLPR*) that is associated with poorer response to SSRIs[1] provides a further rationale for this strategy and suggests that it may be possible to identify those patients most likely to benefit from a noradrenergic intervention.[2,3]

One approach to patients with residual symptoms after adequate treatment with an SSRI could be to stop the SSRI and start an antidepressant with a different pharmacologic mechanism. However, as many patients will have some, albeit incomplete, benefit with SSRI monotherapy, another approach is to add a second agent with a pharma-

cologic mechanism different from the SSRI. Evidence has been reported[4] of superior results among patients treated with a combination of fluoxetine and desipramine compared with those treated with fluoxetine alone, and data from some meta-analyses have suggested that therapy with dual reuptake inhibitors has efficacy advantages over SSRI monotherapy.[5] However, the value of a sequential add-on approach—adding a noradrenergic agent following adequate treatment with an SSRI—has not been demonstrated under controlled conditions.[6]

Atomoxetine is a norepinephrine reuptake inhibitor that has been studied primarily for the treatment of attention-deficit/hyperactivity disorder (ADHD). Studies in patients with depression were conducted with atomoxetine early in its clinical development but did not demonstrate efficacy (Lilly Research Laboratories, data on file). However, the doses used in most of these studies were lower than those found to be efficacious in ADHD (80 mg in adults), and coupled with the fact that positive controls (e.g., desipramine) in those studies also were not superior to placebo, the results are difficult to interpret. Data from a case series suggest that atomoxetine might be of benefit as an add-on therapy to first-line antidepressant treatment,[7] but no controlled studies addressing this question have been reported. We present here the results of an assessment of the efficacy of adding atomoxetine to sertraline in patients with residual depressive symptoms after an initial trial of sertraline monotherapy.

METHOD

This multicenter study was conducted at 15 academic and private research sites in the United States from June 18, 2003, to January 28, 2005. Patients were eligible to participate if they were 18 years of age or older, currently had major depressive disorder, and had at least 1 prior episode of depression in the previous 3 years, as assessed by clinical interview and confirmed by the Structured Clinical Interview for DSM-IV[8] and a symptom severity rating ≥ 18 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17).[9] Baseline evaluations included medical history; physical and laboratory examinations, including routine chemistries, complete blood count, and urinalysis; electrocardiogram; and *5-HTTLPR* genotype (Genaissance Pharmaceuticals, Morrisville, N.C.). Patients with serious medical illness, psychosis, bipolar disorder, or ADHD were ineligible to participate, as were patients with treatment-resistant depression (defined as depression unresponsive to trials with 3 or more pharmacologic treatments). All patients provided written informed consent to participate. The study was reviewed and approved by each site's institutional review board and was conducted in keeping with the principles of the Declaration of Helsinki.[10]

The initial phase of the study was an 8-week assessment of response to monotherapy with sertraline, administered as a single daily dose initiated at 100 mg/day and increased in 50-mg increments to a maximum of 200 mg/day, based on investigator-assessed efficacy and tolerability. Patients who completed the 8-week period with a score > 4 on the Maier and Philipp core mood severity subscale (MPS)[11] of the HAM-D-17 were randomly assigned under double-blind conditions to receive 8 weeks of sertraline combined with atomoxetine 40 to 120 mg/day or to sertraline combined with placebo. The dose of sertraline during randomized treatment was fixed at 150 mg/day or, for patients unable to tolerate 150 mg/day during the monotherapy phase, 100 mg/day. Atomoxetine was initiated at 40 mg/day and could be increased in 40-mg increments to a maximum of 120 mg/day, based on investigator-assessed efficacy and tolerability. To minimize rating bias, investigators and patients were blind to the symptom severity threshold for randomization. To preserve this blinding, patients who met the response criteria (MPS ≤ 4 and no single item > 1) after the initial 8 weeks continued sertraline monotherapy in the randomized phase but were not included in the analyses of results from the randomized phase of the trial.

The protocol-specified primary outcome measure was a treatment comparison of the mean change at end point on the MPS. Secondary measures included mean change on the HAM-D-17 and the Clinical Global Impressions-Severity of Illness scale (CGI-S)[12] as well as categorical analyses using 3 prospectively defined categories: remitters (end point MPS score ≤ 4 and no single item > 1), nonresponders (< 30% reduction from baseline in symptom severity as measured by the change in MPS), and patients with some improvement in symptom severity who did not reach the remission threshold, referred to in this report as partial responders (reduction severity from baseline greater than 30% as measured by the change in MPS score but end point MPS > 4). We also conducted analyses by *5-HTTLPR* genotype. Safety was assessed at each visit by open-ended questioning.

The primary analysis was the comparison of change from randomization to end point in the MPS between sertraline/placebo (SRT/PBO) and sertraline/atomoxetine (SRT/ATX) using an analysis of covariance (ANCOVA) model with terms for treatment, investigator site, and baseline MPS score for all randomly assigned patients with a baseline and at least 1 postbaseline observation. Continuous secondary outcome measures were also assessed using an ANCOVA model with terms for treatment, investigator site, and baseline score for all randomly assigned patients with a baseline and at least 1 postbaseline observation. Remission and partial response rates at end point were compared using the Fisher exact test. All tests were conducted using a 2-sided significance level of .05, and because the protocol specified a primary

Table 1. Patient Characteristics

Characteristic	Open-Label Monotherapy With Sertraline (N = 276)	Randomized Treatment: Sertraline/ Atomoxetine (N = 72)	Randomized Treatment: Sertraline/ Placebo (N = 74)
Male/female, N	96/180	25/47	25/49
Age, mean (SD), y	42.4 (13.3)	44.0 (12.3)	45.5 (13.8)
Concurrent diagnoses, N (%)			
Anxiety (any subtype)	16 (5.8)	2 (2.8)	7 (9.5)
PTSD	3 (1.1)	1 (1.4)	0 (0.0)
5-HTTPR genotype, N (%)[a]			
l/*l*	79 (30.3)	22 (32.4)	16 (22.9)
l/*xl*	3 (1.2)	2 (2.9)	0 (0.0)
s/*l*	126 (48.3)	32 (47.1)	36 (51.4)
s/*xl*	2 (0.8)	0 (0.0)	1 (1.4)
s/*s*	51 (19.5)	12 (17.7)	17 (24.3)

[a]For sertraline monotherapy, N = 261; for sertraline/atomoxetine therapy, N = 68; for sertraline/placebo therapy, N = 70.
Abbreviations: 5-HTTPR = serotonin transporter promoter region, l = long, PTSD = posttraumatic stress disorder, s = short, xl = extralong.

Table 2. Efficacy Outcomes in Patients Receiving Sertraline Monotherapy

Measure	Study Entry, All Entered (N = 276)	End Point, All Patients[a] (N = 250)	End Point, Completers (N = 227)
HAM-D-17 total score, mean (SD)	22.9 (3.7)	12.4 (7.3)	11.7 (6.9)
Maier and Philipp score, mean (SD)	12.2 (2.0)	6.2 (4.1)	5.9 (3.9)
CGI-S score,[b] mean (SD)	4.5 (0.6)	…	2.9 (1.3)
Remission, N (%)	…	72 (28.8)	70 (30.8)
Partial response, N (%)	…	105 (42.0)	100 (44.1)
No response, N (%)	…	73 (29.2)	57 (25.1)

[a]Last observation carried forward.
[b]CGI-S measured at end point only for completers (N = 227).
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.
Symbol: … = not applicable.

outcome measure, other analyses were considered secondary and hence exploratory; thus, no correction for multiple comparisons was made. Adverse event rates and percentages of abnormal laboratory values were compared using the Fisher exact test at the .05 significance level.

RESULTS

After screening, 276 patients met entry criteria and entered the open-label sertraline treatment phase of the study. Patient characteristics are summarized in Table 1. During sertraline monotherapy, 227 (82.2%) patients completed treatment, 17 (6.2%) were lost to follow-up, and 24 (8.7%) discontinued due to an adverse event. Other reasons for discontinuation included lack of efficacy, protocol violations, and scheduling or other personal problems. Of the completers, 157 were nonresponders or partial responders, and, of these, 146 continued into the randomized portion of the study (SRT/ATX, N = 72; SRT/PBO, N = 74). Completion rates for the 8-week, randomized treatment period were similar between groups (59/72 [81.9%] SRT/ATX patients, 61/74 [82.4%] SRT/PBO patients; p > .999). There was no difference between groups on the primary outcome measure at end point (Table 2) or at any postrandomization visit. There were no differences between groups in the prospectively specified secondary measures for mean change in symptoms or categorical definitions of response (Tables 2 and 3).

In the SRT/ATX group, the mean ± SD final doses of ATX and SRT were 66.1 ± 30.1 mg/day and 146.0 ± 27.4 mg/day, respectively, and in the SRT/PBO group, the mean ± SD final SRT dose was 143.9 ± 29.8 mg/day. There was no difference between groups in discontinuations related to adverse events (SRT/ATX 7/72 [9.7%], SRT/PBO 4/74 [5.4%], p = .364) or in discontinuations for any other reason. Among adverse events reported by at least 5% of either group, a significantly greater proportion of patients in the SRT/ATX group reported dry mouth, insomnia, and constipation compared with the SRT/PBO group (Table 4). There was no evidence of serious safety concerns or clinically meaningful changes in laboratory outcomes in either group. Five patients in each treatment group had sustained worsening of suicidal ideation at end point, as assessed by HAM-D-17 Item 3. Two of the SRT/PBO patients had a worsening of 2 points, while the other 8 had a 1-point increase.

Genotype for *5-HTTLPR* was available for 261 of the 276 patients who entered the study, and it did not affect response to sertraline monotherapy (*l*/*l* or *l*/*xl* genotype: 25/74 [33.8%] remitters, 29/74 [39.2%] partial responders, 20/74 [27.0%] nonresponders; *l*/*s* or *xl*/*s* genotype: 32/116 [27.6%] remitters, 53/116 [45.7%] partial responders, 31/116 [26.7%] nonresponders; *s*/*s*: 11/47 [23.4%] remitters, 18/47 [38.3%] partial responders, 18/47 [38.3%] nonresponders; Fisher exact p = .493). There was no effect of genotype on discontinuations due to adverse events during the monotherapy treatment period (*l*/*l*, *s*/*l*, *l*/*xl*, or *s*/*xl*: 19/210 [9.0%]; *s*/*s*: 4/51 [7.8%]; Fisher exact p > .999) or any reason (*l*/*l*, *s*/*l*, *l*/*xl*, or *s*/*xl*: 75/210 [35.7%]; *s*/*s*: 19/51 [37.3%]; Fisher exact p = .872). Following randomization, among sertraline nonresponders and partial responders with an *s*/*s* genotype, addition of atomoxetine was associated with significantly more remissions compared with placebo (SRT/ATX 9/11 [81.8%], SRT/PBO 5/14 [35.7%], p = .042). No treatment effect was observed in patients with other genotypes (Table 5).

DISCUSSION

The rationale for adding atomoxetine following an incomplete response to an SSRI is based on the fact that

Table 3. Efficacy Outcomes in Randomized Treatment Group

Measure	Study Entry[a] Sertraline/ Atomoxetine (N = 72)	Study Entry[a] Sertraline/ Placebo (N = 74)	Randomization Phase[a] Sertraline/ Atomoxetine (N = 70)	Randomization Phase[a] Sertraline/ Placebo (N = 71)	End Point[a] Sertraline/ Atomoxetine (N = 70)	End Point[a] Sertraline/ Placebo (N = 71)	p Value[b]
HAM-D-17 total score	23.4 (3.5)	23.1 (4.3)	14.3 (5.7)	15.0 (5.5)	9.3 (6.6)	10.9 (7.2)	.378
Maier and Philipp score	12.4 (1.6)	12.5 (2.4)	7.7 (3.1)	8.1 (3.1)	4.8 (3.9)	5.4 (3.9)	.597
CGI-S score	4.5 (0.7)	4.6 (0.7)	3.3 (1.0)	3.5 (0.9)	2.4 (1.3)	2.7 (1.4)	.376

[a]Values expressed as mean (SD).
[b]ANCOVA for mean change from randomization to end point for all patients with at least 1 postrandomization observation.
Abbreviations: ANCOVA = analysis of covariance, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

Table 4. Adverse Events During Double-Blind Treatment

Event[a]	Sertraline/ Atomoxetine (N = 72), N (%)	Sertraline/ Placebo (N = 74), N (%)	p Value[b]
Dry mouth	16 (22.2)	1 (1.4)	< .001
Fatigue	6 (8.3)	4 (5.4)	.530
Headache	4 (5.6)	6 (8.1)	.745
Nausea	7 (9.7)	3 (4.1)	.206
Diarrhea	4 (5.6)	5 (6.8)	> .999
Insomnia	8 (11.1)	1 (1.4)	.017
Depressed mood	3 (4.2)	5 (6.8)	.719
Increased sweating	6 (8.3)	2 (2.7)	.163
Constipation	7 (9.7)	0 (0.0)	.006
Dizziness	5 (6.9)	1 (1.4)	.114
Flatulence	1 (1.4)	4 (5.4)	.367
Nasopharyngitis	1 (1.4)	4 (5.4)	.367
Tremor	1 (1.4)	4 (5.4)	.367
Feeling jittery	4 (5.6)	0 (0.0)	.057

[a]All events reported by ≥ 5% of either group.
[b]Fisher exact test.

Table 5. Efficacy Outcomes: Rates of Remission at End Point

Patient group	Sertraline/ Atomoxetine	Sertraline/ Placebo	p Value[a]
All randomly assigned patients, N (%)	29/72 (40.3)	28/74 (37.8)	.865
Sertraline nonresponders, N (%)	5/26 (19.2)	7/28 (25.0)	.747
Partial sertraline responders, N (%)	24/46 (52.2)	21/46 (45.7)	.677
l/*l* or *s*/*l* genotype, N (%)	17/53 (32.1)	20/52 (38.5)	.544
s/*s* genotype, N (%)	9/11 (81.8)	5/14 (35.7)	.042

[a]Fisher exact test.
Abbreviations: l = long, s = short.

some norepinephrine transporter (NET) inhibitors are efficacious antidepressants (e.g., desipramine, reboxetine) and that adding a second, nonserotonergic pharmacologic mechanism could provide improved symptom relief. To our knowledge, only 1 controlled study has assessed the value of adding a noradrenergic agent to patients identified as SSRI poor responders, and it did not demonstrate a drug-specific effect.[6] The results of our study are consistent with those reported by Fava et al.[6] and do not support adding atomoxetine to an SSRI when patients fail to respond adequately to monotherapy.

Several factors could account for this outcome. It may be the case that whatever renders depressed patients poorly responsive to serotonergic intervention also makes them resistant to noradrenergic intervention, perhaps because of common downstream pathways. It could be that there is something specific about atomoxetine that makes it ineffective in this setting and that a different NET inhibitor such as desipramine or reboxetine would have demonstrated efficacy, perhaps because of a higher affinity for other non-NET pharmacologic targets compared with atomoxetine. The failure to observe a difference between treatment groups may be partially accounted for by the fact that the remission criterion was drawn from the MPS, which assesses only core mood items, or it could also reflect relative treatment resistance in the study population, perhaps related to the exclusion of patients experiencing their first depressive episode. However, the remission rate of 29% after the initial period of sertraline treatment does not suggest a particularly treatment-resistant group. Further, the fact that overall HAM-D-17 scores were on average about double MPS scores suggests that the MPS remission criterion of 4 would correspond to a HAM-D-17 score of about 8, which is a commonly used criterion for remission. With respect to the observed outcomes, it could be that the initial remission criterion was too stringent and that some patients categorized as partial responders actually responded to monotherapy reasonably well and could therefore only have had limited benefit from any further intervention, creating a "floor effect" during randomized treatment. However, the fact that outcomes were not different when analyses were restricted to the most symptomatic patients (nonresponders) suggests that using a different symptom threshold for partial responders would not have yielded different outcomes.

Dropout during the initial 8-week period was high, raising the possibility that selection bias affected the outcomes. Such a bias might have been particularly likely if dropouts during the initial period were weighted toward those patients with an *s*/*s* genotype; however, the data did not demonstrate a difference in dropouts for adverse events or any other reason relative to genotype. Other

aspects of the design or conduct of this study could also account for the observed outcomes—for example, the dose range of atomoxetine used was that associated with efficacy in adults with ADHD and was associated with a characteristic adverse event profile. That said, we cannot rule out the possibility that, for example, a higher dose of atomoxetine or a lower dose of sertraline could have had different results, or that some patients who did not show improvement at 8 weeks might have responded after a longer period. Similarly, although a multicenter trial allows for the inclusion of large numbers of patients, which should improve the ability to detect effects, the use of multiple different sites is also a source of variance, which could have offset value of the increased sample size and obscured small treatment effects.

We also cannot exclude the possibility that we failed to observe a difference masked by sample size, nonspecific effects, or other causes. However, in the subgroup of patients who had inadequate responses after sertraline monotherapy, approximately 75% in each treatment group were nonremitters after random assignment, suggesting there was not a large, nonspecific response. Taken together with the absence of any trend towards a difference in outcome between groups, we believe it is unlikely that a true difference existed but was not detected.

Several investigators have reported that genetic polymorphisms in the serotonin transporter are associated with alterations in response to SSRIs,[1,13] a finding not replicated in all studies.[14,15] One report has also suggested that *5-HTTLPR* genotype is associated with differential susceptibility to SSRI-associated adverse events.[16] This study did not replicate either of these findings, a result for which we cannot account, except to note that it could be related to unknown factors that obscured the effect of genotype. By contrast, during the randomized portion of the trial, patients with an *s*/*s* genotype had a significantly better response to SRT/ATX than to SRT/PBO, an effect not observed for the other genotypes. Given the absence of a genotype effect during acute treatment and the small number of patients with the *s*/*s* genotype during the double-blind comparison, these results could represent a random finding. However, taken cautiously and treated as preliminary, they are of interest and, if replicated, could provide a means for identifying patients likely to benefit from the addition of atomoxetine.

CONCLUSION

In summary, for patients with prospectively ascertained nonresponse or partial responses to an 8-week trial of sertraline at doses up to 200 mg/day, the addition of atomoxetine at doses up to 120 mg did not confer additional benefit compared with placebo in the overall group. In the small group of patients with an *s*/*s 5-HTTLPR* genotype, those who received atomoxetine in addition to sertraline were significantly more likely to respond than those who continued sertraline monotherapy.

Drug names: atomoxetine (Strattera), desipramine (Norpramin and others), fluoxetine (Prozac and others), sertraline (Zoloft and others).

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REFERENCES

1. Smeraldi E, Zanardi R, Benedetti F, et al. Polymorphism within the promoter of the serotonin transporter gene and antidepressant efficacy of fluvoxamine. Mol Psychiatry 1998;3:508–511
2. Nelson JC. Treatment of refractory depression. Depress Anxiety 1997;5:165–174
3. Potter WZ, Schmidt ME. Noradrenergic and other new antidepressants. In: Halbreich U, Montgomery S, eds. Pharmacotherapy for Mood, Anxiety and Cognitive Disorders. Washington, DC: American Psychiatric Press; 2000:237–254
4. Nelson JC, Mazure CM, Jatlow PI, et al. Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. Biol Psychiatry 2004;55:296–300
5. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234–241
6. Fava M, Rosenbaum JF, McGrath PJ, et al. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. Am J Psychiatry 1994;151:1372–1374
7. Carpenter L. Augmentation with open-label atomoxetine for partial or nonresponse to antidepressants. J Clin Psychiatry 2005;66:1234–1238
8. First MB, Spitzer GM, Spitzer RL, et al. Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version. New York, NY: Bio-

metrics Research, New York State Psychiatric Institute; 2000
9. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
10. World Medical Association. Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, 2000. Available at: http://www.wma.net/e/policy/b3.htm. Accessibility verified February 5, 2007
11. Maier W, Philipp M. Improving the assessment of depressive states: a reduction of the Hamilton Depression Scale. Pharmacopsychiatry 1985;18:114–115
12. Guy W. ECDEU Assessment Manual for Psychopharmacology, revised. Bethesda, Md: US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md. National Institute of Mental Health; 1976:218–222
13. Pollock BG, Ferrell RE, Mulsant BH, et al. Allelic variation in the serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression. Neuropsychopharmacology 2000;23:587–590
14. Kim DK, Lim SW, Lee S, et al. Serotonin transporter gene polymorphism and antidepressant response. NeuroReport 2000;11:215–219
15. Yoshida K, Ito K, Sato K, et al. Influence of the serotonin transporter gene-linked polymorphic region on the antidepressant response to fluvoxamine in Japanese depressed patients. Prog Neuropsychopharmacol Biol Psychiatry 2002;26:383–386
16. Murphy GM Jr, Hollander SB, Rodrigues HE, et al. Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. Arch Gen Psychiatry 2004;61:1163–1169