Augmentation With Open-Label Atomoxetine for Partial or Nonresponse to Antidepressants

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Background: Atomoxetine is a selective norepinephrine reuptake inhibitor currently approved for the treatment of attention-deficit/hyperactivity disorder. Other compounds that enhance synaptic norepinephrine have shown efficacy as antidepressant monotherapies and as augmentation agents. This case series study examined the role of atomoxetine in antidepressant augmentation.

Method: Fifteen adult outpatients with primary DSM-IV Axis I depressive disorders received open-label atomoxetine augmentation following partial response or nonresponse to at least 8 weeks of standard antidepressant pharmacotherapy. Atomoxetine 40 mg/day was added to ongoing medication regimens and titrated according to clinical response. Atomoxetine was systematically offered to patients from July through October 2003.

Results: Eleven patients (73%) completed at least 6 weeks of atomoxetine augmentation. Mean endpoint dose was approximately 80 mg/day. Nine patients (60%) met criteria for positive categorical response. Inventory of Depressive Symptomatology–Self-Report scores decreased significantly from baseline to endpoint, and clinician ratings of social and occupational functioning increased. There were no significant changes in heart rate or blood pressure, and the most common side effect was activation. A modest but significant drop in body mass index was observed ($p = .025$), and a subset (6/15; 40%) of patients reported improved sexual function.

Conclusion: More studies are warranted to evaluate the potential utility of atomoxetine for antidepressant augmentation.

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The currently available armamentarium of drugs approved by the U.S. Food and Drug Administration (FDA) remains inadequate for the treatment of many individuals with depressive disorders. It has been estimated that as many as 46% of patients do not respond to an adequate trial of antidepressant medication monotherapy.[1,2] Side effects limit many patients from achieving or sustaining monotherapy treatment with an antidepressant at a sufficient dose to produce maximal clinical benefit.[3,4] Even when antidepressant pharmacotherapy is undertaken at the optimal dosage, responders to treatment are commonly left with residual symptoms.[5–7] Failure to reach full symptom remission is associated with poorer long-term functional outcomes and a higher risk for relapse.[6,8]

While the term *treatment-resistant depression* (TRD) has been more stringently applied to cases of major depression that have failed to respond to 2 or more adequate trials of antidepressant treatments from different classes,[9] TRD has also been conceptualized with a staging system analogous to that used for cancer.[10] Patients with major depression who have failed to experience remission following an adequate trial of a single antidepressant medication may be classified as having stage 1 resistance, while those who continue in a depressive episode following trials of antidepressants from 2 different classes and electroconvulsive therapy would be considered as having stage 5 resistance. Survey data from psychiatrists indicate that adding secondary psychotropic agents to the ongoing antidepressant regimen is a common practice when opti-

mal outcome is not achieved with antidepressant monotherapy.[11] While evidence-based treatment guidelines and algorithms for TRD are the goal of large-scale research projects currently underway,[12] clinicians presently faced with the dilemma of what to do next when a single antidepressant trial fails to produce full depressive symptom resolution must make such decisions with a paucity of controlled data. Some of the agents most commonly employed for antidepressant augmentation are lithium,[13,14] atypical antipsychotics,[15–17] thyroid hormone supplements,[18,19] and stimulants.[20] Addition of a second antidepressant with a different neurotransmitter or target receptor mechanism than that assumed to be responsible for the partial response observed with the primary antidepressant has also been described as beneficial for some patients with TRD.[21–23] Unfortunately, the improvements in depressive symptomatology gained as a result of augmentation therapy may not always weigh favorably against the burden of additional or exaggerated side effects produced as a result of the introduction of another psychotropic medication.

Atomoxetine is a selective norepinephrine reuptake inhibitor (SNRI) that is currently FDA approved and marketed for the treatment of attention-deficit/hyperactivity disorder in the adult and pediatric population.[24,25] Although this compound has not been fully developed for use as an antidepressant,[26–28] a review of its primary mechanism of action led us to speculate about its potential utility as an augmentation agent for patients with TRD. Another SNRI, reboxetine, has been studied and marketed extensively in Europe, where it has shown significant antidepressant effects in drug-naive and SSRI-resistant patients, both as monotherapy[29–31] and as an augmentation agent.[32] The well-established tricyclic drug desipramine is also thought to exert its primary antidepressant effects through increasing norepinephrine at the neuronal synapse. The addition of desipramine to pharmacotherapy with a selective serotonin reuptake inhibitor (SSRI), and the resulting synergy from activation of dual (norepinephrine and serotonin) neurotransmitter systems, has been interpreted as an effective pharmacologic strategy for TRD.[13,22,33] Experience with reboxetine, desipramine, and other drugs that enhance noradrenergic neurotransmission supports the notion that atomoxetine may have a role in the treatment of depression. Other than 1 recently published letter describing 3 cases of atomoxetine addition to SSRI therapy for residual symptoms of depression,[32] no published data are available to address this hypothesis. The description of a case series systematically assessed and presented here reflects a first step in evaluating the potential utility of atomoxetine for antidepressant augmentation.

METHOD

Collection of case series data describing systematic assessment of response to open-label augmentation treatment with atomoxetine in depressive disorders was approved by the Butler Hospital Institutional Review Board. Butler Hospital Mood Disorders Research Clinic investigators prospectively implemented a simple battery of clinician- and self-report measures to routinely monitor outcomes in a naturalistic outpatient clinic setting where a variety of pharmacologic strategies were being used to treat TRD. The sample was drawn from adult outpatients with a primary DSM-IV Axis I depressive disorder treated by a research psychiatrist (N.M. or L.L.C.) with "physician's choice" pharmacotherapy and followed with standard clinic care (visit interval determined as clinically indicated by patient's status rather than by protocol). Patients were considered candidates for augmentation pharmacotherapy if they were judged to have an inadequate response despite a minimum of 8 weeks' treatment with the maximum recommended dosage of an approved antidepressant drug. *Inadequate response* was defined as persistent depressive symptoms of at least moderate severity, corresponding to "moderately ill" or worse on the Clinical Global Impressions (CGI)-Severity of Illness scale[34] as rated by both the clinician and the patient.

In the context of reviewing treatment options for TRD, atomoxetine was systematically offered as an open-label augmentation trial to appropriate adult clinic patients from July through October 2003. Risks and benefits of adjunctive atomoxetine were discussed with each patient, and a supply of atomoxetine drug samples was made available to those who elected to undertake the trial. Atomoxetine 40 mg/day was added to the ongoing medication regimen and subsequently titrated in open fashion, as tolerated, to a maximum of 120 mg daily. Follow-up appointments occurred as routine clinic visits, typically every 2 to 3 weeks or as otherwise indicated. At each clinic visit, routine assessments performed by the clinician included the CGI scales for illness severity and improvement,[34] the Global Assessment Scale,[35] and the Social and Occupational Functioning Assessment Scale.[36] Weight and vital signs (blood pressure, pulse, and respiratory rate) were also recorded. Before meeting with their clinicians, patients routinely completed the Inventory of Depressive Symptomatology–Self-Report (IDS-SR)[37] and the SAFTEE[38,39] for side effects.

Clinical and demographic data were collected from outpatient medical records when the last of 15 patients had completed an atomoxetine trial. Data from serial clinic visits during the atomoxetine trial were grouped to approximate time intervals from baseline and to allow for examination of response patterns over time. Data from the second clinic visit correspond to days 8 through 21 on drug (labeled together as "week 1–3"). Assessments from days 27 through 36 were grouped together to represent the "week 4–5" time point, while data from days 40 through 49 were grouped together to represent "week 6–7," and data from days 56 through 73 together comprise the final

Table 1. Baseline Clinical Characteristics of Patient Sample in Atomoxetine Antidepressant Augmentation Trial

Characteristic	N = 15
Age, mean (range), y	41.5 (21–54)
Gender, N (%)	
Male	6 (40)
Female	9 (60)
Weight, mean (range), lb[a]	172 (118–242)
BMI, mean (range), kg/m^{2a}	28 (19.5–43)
Diagnosis, N (%)	
Major depressive disorder	12 (80)
Depressive disorder, not otherwise specified	2 (13)
Bipolar II disorder	1 (7)
Primary antidepressant, N (%)	
SSRI[b]	8 (53)
SSRI + bupropion[b]	3 (20)
Venlafaxine	3 (20)
Bupropion	1 (7)
Duration of primary antidepressant, mean (range), wk	121.5 (8–368)
CGI-Severity of Illness scale, N (%)	
Moderate	5 (33)
Marked	7 (47)
Severe	3 (20)

[a]One outlier, a male subject weighing 399 lb, was removed from analysis of weight change.
[b]SSRIs augmented included citalopram, escitalopram, paroxetine, and sertraline.
Abbreviations: BMI = body mass index, CGI = Clinical Global Impressions, SSRI = selective serotonin reuptake inhibitor.

time point, "week 8–10." Outcomes were examined with last observations carried forward in all analyses. *Categorical response* was defined as a 50% decrease in IDS-SR score from baseline. Paired t tests (2-tailed) were used to compare baseline with endpoint values. Side effects that emerged as moderate or severe, or worsened to any degree, during atomoxetine augmentation were captured as simple frequencies. When body mass index (BMI) and weight data were examined in post hoc analyses, 1 outlier, a man weighing 399 lb., was excluded from analysis.

RESULTS

Patients who elected to undertake atomoxetine augmentation agreed to hold all other psychotropic medication doses stable during the trial. Clinical characteristics for the sample are presented in Table 1. For N = 15 in this series, the mean ± SD duration of atomoxetine augmentation was 44.5 ± 23.3 days (range, 3–83 days). Eleven (73%) of 15 patients completed ≥ 6 weeks of augmentation, and 4 discontinued before 6 weeks. Discontinuation of atomoxetine occurred at the request of the patient and/or recommendation of the psychiatrist. Three patients (20%) discontinued due to side effects (nausea or vomiting) and 1 (7%) discontinued due to lack of efficacy. Final mean ± SD atomoxetine dose was 79.0 ± 38.4 mg/day (range, 25–120 mg/day).

Evidence of clinical benefit during atomoxetine augmentation was statistically apparent on every clinical outcome measure (Table 2). The categorical response rate was 60% (N = 9), and 47% (N = 7) experienced remission, defined as an IDS-SR score of less than 15 at endpoint. Self-reported symptom scores on the IDS-SR decreased significantly from baseline to each visit (Figure 1).

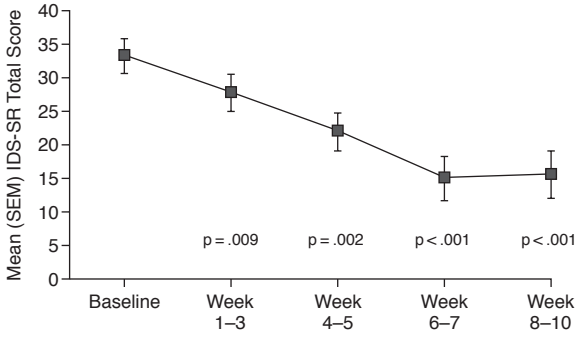
Atomoxetine augmentation was generally well-tolerated in this open-label trial. There were no significant changes in heart rate or blood pressure. Weight (BMI) decreased significantly during atomoxetine augmentation (from 27.9 ± 6.3 to 27.7 ± 6.1 kg/m^2, t = 2.5, p = .025), representing a mean loss of 1.4 lb. Sexual function (interest, arousal, and orgasm) improved in a subset of patients (N = 6, 40%) during atomoxetine

Table 2. Outcome Measures in Atomoxetine Antidepressant Augmentation Trial

Measure	Baseline N = 15	Endpoint N = 15	p Value (2-tailed)
Categorical response (50% decrease on IDS-SR), N (%)	N/A		N/A
Responder		9 (60)	
Nonresponder		6 (40)	
Remission (IDS-SR score < 15), N (%)		7 (47)	
GAS score, mean (SD)[a]	57.6 (4.9)	65.4 (7.1)	.001
SOFAS score, mean (SD)[a]	57.1 (6.1)	66.1 (8.0)	< .001
IDS-SR, total score, mean (SD)	33.4 (10.3)	15.7 (13.7)	.001
Clinician-rated CGI-S score, mean (SD)[b]	4.9 (0.7)	3.7 (1.2)	.001
Patient-rated CGI-S score, mean (SD)[b]	4.9 (0.7)	3.6 (1.3)	.003

[a]Range, 0–100.
[b]Range, 1–7.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, GAS = Global Assessment Scale, IDS-SR = Inventory of Depressive Symptomatology–Self-Report, SOFAS = Social and Occupational Functioning Assessment Scale.

Figure 1. Depression Symptom Scores (IDS-SR) Plotted Over Time[a]



[a]p Values reflect significance for paired t tests comparing baseline values with last-observation-carried-forward values at each time point.
Abbreviation: IDS-SR = Inventory of Depressive Symptomatology–Self-Report.

augmentation. Side effects on the SAFTEE self-report checklist that emerged or worsened at any time during the atomoxetine trial included nightmare or sleep disturbance, drooling or increased salivation, trouble catching breath/hyperventilation, diarrhea, difficulty starting urination, or frequent urination (N = 1 each); nausea or vomiting, delayed orgasm, blurred vision, trouble with concentration, trouble sitting still, poor coordination, or muscle twitching (N = 2 each); excessive sweating, feeling drowsy, feeling irritable, numbness or tingling, stuffy nose, rapid heartbeat, loss of sexual interest, or problems with sexual arousal (N = 3 each); dizziness or faintness, trouble sleeping, abnormal sensations, dry mouth, appetite decrease, or weight loss (N = 4 each); and "feeling nervous" or "feeling hyper" (N = 5 each). None of these side effects was scored as severe.

DISCUSSION

Data from this open-label case series study of antidepressant augmentation with the SNRI atomoxetine suggest that atomoxetine is beneficial in reducing depressive symptoms in some patients who have had partial response or nonresponse to standard antidepressant trials. Nine (60%) of 15 subjects met categorical response criteria, and all of them endorsed improvement on at least 1 of the 2 core mood items from the IDS-SR (feeling sad or feeling irritable). It is unlikely that the magnitude of symptom resolution reported by the responders in this study is attributable to nonspecific improvements in concentration and energy that might be seen with stimulant use. Since all but 1 subject had been taking their primary antidepressant at least 23 weeks before starting the augmentation trial, there is a low probability that the observed clinical improvements can be attributed to extension of the initial pharmacotherapy regimens.[40] The synergistic activation of dual (norepinephrine and serotonin) neurotransmitter systems may have contributed to the positive outcomes we observed, but since not all of the patients in this series were treated solely with SSRIs before addition of atomoxetine, the study is limited in its ability to provide support for any specific mechanism of action.

Our observations support the preliminary conclusion that moderate doses (average 80 mg/day) of atomoxetine are generally well tolerated when combined with newer (i.e., not tricyclic or monoamine oxidase inhibitor) antidepressant medications. Notable exceptions were seen in 3 subjects who were not able to tolerate gastrointestinal upset associated with atomoxetine augmentation (40 mg/day) beyond 3 or 4 days. Two of those subjects were taking sertraline; the other was taking bupropion. It is possible that these individuals are among the approximately 7% of the Caucasian population vulnerable to experiencing a 5-fold higher peak concentration of atomoxetine as a consequence of inherent poor metabolism of cytochrome CYP2D6.[41] Weak inhibition of CYP2D6 by sertraline is a less plausible explanation for poor tolerability observed in these individuals, as atomoxetine augmentation of paroxetine, a more potent inhibitor of the same enzyme, did not produce exaggerated side effect profiles in 4 patients in our sample. Nevertheless, practitioners electing this strategy for treatment-resistant depression should remember that augmentation of paroxetine or fluoxetine may produce 3- to 4-fold increases in atomoxetine concentrations (relative to those measured for atomoxetine monotherapy with the same doses)[41] and adjust starting doses accordingly.

Antidepressant augmentation therapy is best implemented with a solid knowledge base regarding the particular risks of specific drug combinations. While the sample size was small and the study was not designed to specifically address such issues, the data provide some preliminary support for the notion that addition of atomoxetine to standard antidepressant therapy may ameliorate side effects such as sexual dysfunction and weight gain. Seven subjects (47%) in our series lost weight (mean = 3.1 lb.), 1 subject gained weight (2 lb.), and the others had no weight change at the end of the atomoxetine trial. Patients who lost weight were taking SSRIs (N = 5) or venlafaxine (N = 2) as their primary antidepressant therapy. Among adults receiving atomoxetine monotherapy, decreased appetite is a fairly common (10%) side effect, but weight loss has been less frequently reported (2%).[41] Another unanticipated observation was reversal of sexual dysfunction (i.e., improved interest, arousal, and orgasm) in 6 patients (40%) taking atomoxetine, presumably via enhanced noradrenergic tone. Larger controlled studies are needed to systematically determine whether atomoxetine offers significant benefits in management of these side effects, as well as to further establish whether atomoxetine is a safe and efficacious agent for widespread use as an adjunct to other antidepressant pharmacotherapies.

Drug names: atomoxetine (Strattera), bupropion (Wellbutrin and others), citalopram (Celexa and others), escitalopram (Lexapro), desipramine (Norpramin and others), fluoxetine (Prozac and others), lithium (Lithobid, Eskalith, and others), paroxetine (Paxil and others), sertraline (Zoloft), venlafaxine (Effexor).

REFERENCES

1. Clinical Practice Guideline, Number 5: Depression in Primary Care, vol 2. Treatment of Major Depression. Rockville, Md: US Dept Health Human Services, Agency for Healthcare Policy and Research; 1993. AHCPR Publication No. 93-0551
2. Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 2003;53:649–659
3. Nemeroff CB. Improving antidepressant adherence. J Clin Psychiatry 2003;64(suppl 18):25–30
4. Greden JF. Unmet need: what justifies the search for a new antidepressant? J Clin Psychiatry 2002;63(suppl 2):3–7
5. Karp JF, Buysse DJ, Houck PR, et al. Relationship of variability in residual symptoms with recurrence of major depressive disorder during maintenance treatment. Am J Psychiatry 2004;161:1877–1884

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6. Kennedy N, Paykel ES. Residual symptoms at remission from depression: impact on long-term outcome. J Affect Disord 2004;80:135–144
7. Boulenger JP. Residual symptoms of depression: clinical and theoretical implications. Eur Psychiatry 2004;19:209–213
8. McIntyre RS, O'Donovan C. The human cost of not achieving full remission in depression. Can J Psychiatry 2004;49(3 suppl 1):10S–16S
9. Rush AJ, Thase ME, Dube S. Research issues in the study of difficult-to-treat depression. Biol Psychiatry 2003;53:743–753
10. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. J Clin Psychiatry 1997;58 (suppl 13):23–29
11. Nierenberg AA. Treatment choice after one antidepressant fails: a survey of northeastern psychiatrists. J Clin Psychiatry 1991;52:383–385
12. Rush AJ, Trivedi M, Fava M. Depression, 4: STAR*D treatment trial for depression. Am J Psychiatry 2003;160:237
13. 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
14. Bschor T, Lewitzka U, Sasse J, et al. Lithium augmentation in treatment-resistant depression: clinical evidence, serotonergic and endocrine mechanisms. Pharmacopsychiatry 2003;36(suppl 3):S230–S234
15. Papakostas GI, Petersen TJ, Nierenberg AA, et al. Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. J Clin Psychiatry 2004;65:217–221
16. Barbee JG, Conrad EJ, Jamhour NJ. The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. J Clin Psychiatry 2004; 65:975–981
17. Kennedy SH, Lam RW. Enhancing outcomes in the management of treatment resistant depression: a focus on atypical antipsychotics. Bipolar Disord 2003;5(suppl 2):36–47
18. Joffe RT, Sokolov ST. Thyroid hormone treatment of primary unipolar depression: a review. Int J Neuropsychopharmacol 2000;3:143–147
19. Joffe RT. The use of thyroid supplements to augment antidepressant medication. J Clin Psychiatry 1998;59(suppl 5):26–29
20. Nierenberg AA, Dougherty D, Rosenbaum JF. Dopaminergic agents and stimulants as antidepressant augmentation strategies. J Clin Psychiatry 1998;59(suppl 5):60–63
21. Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry 2002;51:183–188
22. 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
23. Lam RW, Hossie H, Solomons K, et al. Citalopram and bupropion-SR: combining versus switching in patients with treatment-resistant depression. J Clin Psychiatry 2004;65:337–340
24. Christman AK, Fermo JD, Markowitz JS. Atomoxetine, a novel treatment for attention-deficit-hyperactivity disorder. Pharmacotherapy 2004;24:1020–1036
25. Garland M, Kirkpatrick P. Atomoxetine hydrochloride. Nat Rev Drug Discov 2004;3:385–386
26. Chouinard G, Annable L, Bradwejn J. An early Phase II clinical trial of tomoxetine (LY139603) in the treatment of newly admitted depressed patients. Psychopharmacology (Berl) 1984;83:126–128
27. Chouinard G, Annable L, Bradwejn J, et al. An early Phase II clinical trial with followup of tomoxetine (LY139603) in the treatment of newly admitted depressed patients. Psychopharmacol Bull 1985;21:73–76
28. Preti A. Tomoxetine (Eli Lilly & Co). Curr Opin Investig Drugs 2002;3:272–277
29. Versiani M, Amin M, Chouinard G. Double-blind, placebo-controlled study with reboxetine in inpatients with severe major depressive disorder. J Clin Psychopharmacol 2000;20:28–34
30. Scates AC, Doraiswamy PM. Reboxetine: a selective norepinephrine reuptake inhibitor for the treatment of depression. Ann Pharmacother 2000;34:1302–1312
31. Montgomery S, Ferguson JM, Schwartz GE. The antidepressant efficacy of reboxetine in patients with severe depression. J Clin Psychopharmacol 2003;23:45–50
32. Berigan TR. Atomoxetine used adjunctively with selective serotonin reuptake inhibitors to treat depression [letter]. Prim Care Companion J Clin Psychiatry 2004;6:93–94
33. Stahl SM, Entsuah R, Rudolph RL. Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. Biol Psychiatry 2002;52:1166–1174
34. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976
35. Endicott J, Spitzer RL, Fleiss JL, et al. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry 1976;33:766–771
36. Goldman HH, Skodol AE, Lave TR. Revising Axis V for DSM-IV: a review of measures of social functioning. Am J Psychiatry 1992;149: 1148–1156
37. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med 1996; 26:477–486
38. Rabkin JG, Markowitz JS, Ocepek-Welikson K, et al. General versus systematic inquiry about emergent clinical events with SAFTEE: implications for clinical research. J Clin Psychopharmacol 1992;12:3–10
39. Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. Psychopharmacol Bull 1986;22: 343–381
40. Licht RW, Qvitzau S. Treatment strategies in patients with major depression not responding to first-line sertraline treatment: a randomised study of extended duration of treatment, dose increase or mianserin augmentation. Psychopharmacology (Berl) 2002;161:143–151
41. Strattera [package insert]. Indianapolis, Ind: Eli Lilly; 2002