Mirtazapine Augmentation in the Treatment of Refractory Depression

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Background: Pharmacotherapeutic strategies that target specific actions at multiple neuronal receptors or cellular components may offer a superior approach for treatment of refractory depression. Mirtazapine is a novel antidepressant which has a mechanism that involves the enhancement of noradrenergic and serotonergic neurotransmission via blockade of α_2-adrenergic autoreceptors and heteroreceptors without activity at the serotonin transporter. Mirtazapine is thus a compelling candidate for augmentation treatment in patients who fail to achieve adequate response with other antidepressant medications.

Method: Twenty patients with DSM-IV major depression or dysthmia who had persistent depressive syndromes despite at least 4 weeks of standard antidepressant pharmacotherapy were given augmentation with mirtazapine (15 to 30 mg p.o. q.h.s.) on an open-label basis. Clinical assessments of status at baseline, 2 weeks, and 4 weeks were used to rate response.

Results: Forty-five percent (N = 9) of the sample were responders at 2 weeks. At the 4 week follow-up, 55% (N = 11) were responders, 30% (N = 6) were nonresponders, and 15% (N = 3) had discontinued treatment owing to side effects. Common side effects included weight gain and sedation.

Conclusion: These data suggest that the addition of mirtazapine may be beneficial for patients who have refractory depression, but side effects are prominent at the doses we used. Controlled trials to further evaluate the efficacy and safety of mirtazapine augmentation are needed.

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The introduction of antidepressant agents with a greater selectivity for the serotonin (5-hydroxytryptamine [5-HT]) neurotransmitter system (e.g., selective serotonin reuptake inhibitors [SSRIs]) has been considered one of the greatest advances in the past few decades of antidepressant drug research and development. Having eliminated direct receptor actions with cholinergic muscarinic receptors, α_1-adrenoceptors, and histamine H_1 receptors, the SSRIs clearly offer a more tolerable pharmacotherapy than did the class of tricyclic antidepressants (TCAs), which preceded them. Although greater tolerability may lead to greater efficacy through enhanced compliance, the SSRIs do not appear to confer a more favorable overall antidepressant response. A meta-analysis[1] comparing SSRI and TCA efficacy shows the two classes are globally similar, but a superiority may exist for TCAs in the treatment of hospitalized and severely depressed patients. It has been hypothesized[2] that the ability to inhibit the reuptake of norepinephrine may have been a key feature of the TCAs that was lost in the SSRIs.

Evidence supporting a role for enhanced norepinephrine function in the mechanism of antidepressant action comes from the use of relatively selective norepinephrine reuptake inhibitors, such as desipramine, in which efficacy as a monotherapy has been clearly established. Electroconvulsive therapy (ECT) also has been shown to increase the release of norepinephrine.[3] Several lines of evidence support the notion that serotonin/norepinephrine synergism may produce the best antidepressant effect for severe depression. Combination drug studies, in which both serotonin and norepinephrine neurotransmitter systems are targeted by treatment with an SSRI plus a selective norepinephrine reuptake inhibitor (e.g., fluoxetine plus desipramine),[4] suggest that the dual action may be better than selectivity for either neurotransmitter alone in a severely ill inpatient population. Another example of the benefit of this approach is reflected in the efficacy of the non-TCA venlafaxine in highly refractory patients.[5] This drug simultaneously inhibits the reuptake of both serotonin and norepinephrine without affinity for those postsynaptic receptors that are responsible for TCA-like side effects.

Norepinephrine neurotransmission is partly under the control of the presynaptic α_2-adrenergic autoreceptors.

When stimulated by norepinephrine, these receptors inhibit the release of norepinephrine into the synapse. Another type of α_2-adrenergic receptor, called a heteroreceptor, is located on the presynaptic terminal end of serotonergic neurons; when stimulated by norepinephrine, it inhibits the cell's release of serotonin. Blockade of α_2-adrenergic autoreceptors and heteroreceptors should, therefore, enhance both norepinephrine and serotonin transmission, respectively.[6] Several clinical reports have suggested that yohimbine, an α_2-adrenoceptor antagonist, potentiates the antidepressant effects of other serotonergic antidepressant drugs[7,8] and ECT.[9]

These findings inspired us to explore the possibility that mirtazapine, a novel antidepressant which has a pharmacologic profile that includes antagonism for the same α_2-adrenoceptors as yohimbine,[10,11] may hold similar potential in the augmentation of standard antidepressants for severe or refractory depression. This preliminary, open-label study describes the efficacy and side effects experienced when mirtazapine was added in 20 patients with depressive disorders nonresponsive to standard antidepressant medication treatment.

METHOD

Twenty consecutive adult outpatients presenting with refractory depressive syndromes were offered and consented to mirtazapine augmentation on an open-label basis. Treatment-refractory depression was defined as failure to experience adequate response (much or very much improvement) to at least 4 weeks of treatment with standard antidepressant medications at the highest tolerable dose. All patients were being seen for medication management in the Butler Hospital Mood Disorders Program in Providence, R.I. Patients were eligible for the study if they met DSM-IV criteria for a primary diagnosis of major depressive disorder or dysthymic disorder. Mirtazapine, 15–30 mg p.o. q.h.s., was added to the primary antidepressant agents, which were continued at the same doses throughout the augmentation period. Concurrent medications (e.g., benzodiazepines, neuroleptics) were similarly continued at their previous doses throughout the augmentation trial.

Information about emergent side effects was obtained through general verbal inquiry at each follow-up contact, which typically occurred biweekly. Consensus Clinical Global Impressions scale (CGI)[12] ratings of baseline severity of depressive illness (CGI-S) and clinical change after 2 and 4 weeks of mirtazapine augmentation (CGI-I) were made by the treating psychiatrist (Z.J.) in conjunction with 2 collaborating research psychiatrists (L.L.C. and L.H.P.), using all available clinical data. Positive response was defined by a CGI-I score of 2 ("much improved") or 3 ("very much improved"), based on clinical presentation relative to preaugmentation baseline state, at 2 and 4 weeks after addition of mirtazapine. Simple descriptive statistics were used to characterize the patient sample and results.

RESULTS

Clinical characteristics for the patient sample (N = 20) are presented in Table 1. The group was composed of 9 (45%) men and 11 (55%) women, with ages ranging from 23 to 60 years (mean ± SD = 44.0 ± 7.2). Most patients had a primary DSM-IV diagnosis of major depressive disorder, but 1 patient with a primary diagnosis of dysthymic disorder was also included in the sample. Mean ± SD age at onset of depressive illness was 38.4 ± 8.4 years, with 0.7 ± 0.9 prior psychiatric hospitalizations and 2.5 ± 1.4 previous antidepressant medication trials. At the time of mirtazapine augmentation, patients had been taking their primary antidepressant agents for 4 to 167 weeks (mean ± SD = 41.9 ± 27.1).

Details about the mirtazapine augmentation phase are presented in Table 2. Primary antidepressants were either SSRIs, venlafaxine, or a combination or desipramine or bupropion with an SSRI or venlafaxine. Common concurrent medications included benzodiazepines (55% of the sample) and conventional neuroleptics (10%); 1 patient was maintained on adjuvant lithium treatment, 1 on adjuvant levothyroxine treatment, and 1 on low-dose trazodone treatment for hypnotic purposes.

CGI-S scores at baseline were rated as "mild" for 1 patient (5% of the sample), "moderate" for 10 patients (50%), and "severe" for 9 patients (45%). The majority (90%) of patients were started and maintained on a mirtazapine dose of 15 mg p.o. q.h.s.; 2 patients (10%) were started on the higher dose of 30 mg/day, while 2 other patients (10%) underwent a dose titration from 15 mg/day to 30 mg/day after 2 weeks.

At the 2-week follow-up point, 45% (N = 9) of the sample met criteria (CGI-I score of 2 or 3) for response and 35% (N = 7) were nonresponders; the remaining patients did not have follow-up visits at week 2, so ratings were not available for that time point. After 4 weeks of mirtazapine augmentation, 55% (N = 11) of the original sample were responders, 30% (N = 6) were nonresponders, and the remaining 15% (N = 3) had discontinued mirtazapine owing to intolerable side effects. Side effects included weight gain, sedation, activation, gastrointestinal distress, appetite increase, hypersomnia, and, in 1 patient, a syndrome characterized by depersonalization and auditory hyperacusis.

Case Vignettes

Mr. A, a 39-year-old man, presented with a 10-month history of depressed mood, anhedonia, decreased libido, insomnia, decreased energy, poor concentration, hopelessness, worthlessness, guilt, and suicidal ideation. He had had similar episodes since childhood, with chronic in-

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Table 1. Patient Characteristics

Patient	Sex	Age (y)	Age at Onset (y)	Number of Hospital Admissions	Number of Past Antidepressant Trials	Number of Weeks Taking Primary Antidepressant Prior to Augmentation	DSM-IV Diagnosis
1	F	47	45	1	2	32.0	Major depressive disorder, recurrent
2	F	60	50	0	3	10.5	Major depressive disorder, recurrent
3	F	40	39	4	4	40.5	Major depressive disorder, recurrent, w/psychotic and melancholic features; bulimia nervosa
4	M	55	53	0	3	32.0	Major depressive disorder, recurrent; generalized anxiety disorder
5	F	44	42	4	3	36.0	Major depressive disorder, recurrent, w/melancholic features
6	M	39	39	0	2	31.0	Major depressive disorder, recurrent
7	F	44	42	0	0	7.0	Major depressive disorder, single episode
8	M	51	23	1	4	73.0	Major depressive disorder, single episode; dysthymic disorder
9	F	53	48	0	1	57.0	Major depressive disorder, single episode; panic disorder with agoraphobia
10	M	50	34	0	3	79.0	Major depressive disorder, recurrent; cocaine dependence in full remission
11	M	45	25	1	4	167.0	Major depressive disorder, recurrent
12	M	51	49	0	8	22.0	Dysthymic disorder
13	F	43	42	0	1	24.0	Major depressive disorder, single episode; dysthymic disorder
14	F	23	20	0	2	47.5	Major depressive disorder, single episode; obsessive-compulsive disorder
15	F	38	30	2	1	6.0	Major depressive disorder, recurrent
16	F	35	32	1	3	76.0	Major depressive disorder, recurrent
17	M	24	23	0	1	18.0	Major depressive disorder, recurrent; dysthymic disorder
18	M	41	40	0	1	65.0	Major depressive disorder, recurrent; dysthymic disorder
19	M	41	36	0	3	4.0	Dysthymic disorder
20	F	56	56	0	0	10.5	Major depressive disorder, recurrent

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tercurrent symptoms of low-grade gloominess and anhedonia, but had never been treated with medication. He began sertraline monotherapy with gradual dose increase to 200 mg/day and experienced a partial response, but insomnia, anhedonia, negative thinking, and anxiety remained prominent. Lithium augmentation was undertaken, with doses up to 1800 mg/day (serum level = 0.6 mEq/L), but he experienced only a mild improvement and developed significant side effects of nausea, diarrhea, and tremor. Lithium was subsequently discontinued, and sertraline was further increased to 250 mg/day, with mild additional benefit. Nearly 13 months after the start of sertraline, mirtazapine, 15 mg/day, was added. At follow-up visits, Mr. A reported significant improvement in the remaining symptoms of anhedonia, apathy, and pessimism, without side effects. He commented, "I am enjoying life and looking forward to every new day."

Ms. B, a 44-year-old divorced woman, presented for her first antidepressant treatment after 2 years of anhedonia, irritability, feeling overwhelmed by day-to-day tasks, weight gain (30 lb), fatigue, and variable sleep disturbance. Her family history was positive for major depression in her mother and in her daughter. In describing her current state, she noted, "I do what I need to do robot-like . . . I wake up tired . . . I go to bed tired . . . I am tired of being tired." She was started on fluoxetine, 20 mg/day, but did not evidence any response after 7 weeks of drug treatment. Her total score on the modified 25-item Hamilton Rating Scale for Depression (HAM-D)[13] was 25 when mirtazapine, 15 mg/day, was added to fluoxetine. She reported dramatic improvement over the first 5 days of mirtazapine augmentation, and her HAM-D score was 0 at the 4-week follow-up visit. She described being in good spirits, feeling ambitious and energetic, and experiencing good sleep.

DISCUSSION

To our knowledge, this is the first published report on the use of mirtazapine augmentation for refractory depression. Mirtazapine was used because it enhances both noradrenergic and serotonergic neurotransmission via targeting of several distinct receptor mechanisms. This work is largely driven by the hypothesis that increased noradrenergic activity provides some synergistic input to serotonergic neurotransmission and the eventual cascade of intracellular events that ultimately lead to antidepressant effect. All of the antidepressant regimens to which mirtazapine was added in our series had the property of inhibiting the serotonin transporter through which serotonin is taken back up into the presynaptic neuron, thereby increasing the available serotonin in the synaptic cleft. Mirtazapine may further contribute to net firing of the postsynaptic serotonin neuron by blocking the inhibitory effects of pre-

Table 2. Response to Mirtazapine Augmentation[a]

Patient	Primary Antidepressant(s), Daily Dose	Concurrent Medications	CGI-S Baseline[b]	2-Week CGI-I[c] Score	2-Week CGI-I[c] Responder	4-Week CGI-I[c] Score	4-Week CGI-I[c] Responder	Side Effects
1	Fluoxetine, 40 mg	Lorazepam	4	n/a		0	No	Weight gain
2	Venlafaxine, 100 mg	Clonazepam	4	0[d]	No	1	No	Weight gain
3	Desipramine, 200 mg; venlafaxine, 75 mg	Clonazepam, lithium, perphenazine	5	n/a		2	Yes	None
4	Sertraline, 200 mg	Clonazepam	4	2	Yes	Discontinued[e]		Weight gain, activation
5	Sertraline, 100 mg; desipramine, 150 mg	Lorazepam, perphenazine, levothyroxine	5	2	Yes	3	Yes	None
6	Fluoxetine, 80 mg	None	5[d]	0	No	Discontinued[e]		Hypersomnia
7	Fluoxetine, 20 mg	None	4	3	Yes	3	Yes	Increased appetite
8	Venlafaxine, 300 mg; fluoxetine, 60 mg	None	4	0[d]	No	0	No	None
9	Paroxetine, 60 mg	Clonazepam	5	n/a		2	Yes	Weight gain
10	Venlafaxine, 150 mg	Lorazepam	5	2	Yes	3	Yes	None
11	Paroxetine, 50 mg	None	4	1	No	2	Yes	None
12	Sertraline, 200 mg; bupropion, 300 mg	None	4	0	No	0	No	Weight gain, sedation
13	Sertraline, 150 mg	Lorazepam	4[d]	1	No	2	Yes	Morning sedation
14	Fluoxetine, 60 mg	Clonazepam	5	2	Yes	2	Yes	Gastrointestinal distress
15	Venlafaxine, 200 mg	Lorazepam	5	1	No	0	No	Sedation
16	Sertraline, 150 mg	Trazodone	5	2	Yes	3	Yes	None
17	Fluoxetine, 20 mg	Lorazepam	5	n/a		0	No	None
18	Sertraline, 250 mg	None	3	3	Yes	3	Yes	None
19	Venlafaxine, 150 mg	None	4	2	Yes	2	Yes	Sedation
20	Paroxetine, 20 mg	None	4	2	Yes	Discontinued[e]		Depersonalization, auditory hyperacusis

[a]Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = CGI-Severity of Illness scale, n/a = data not available.
[b]Baseline CGI-S scores: 1 = normal, not at all mentally ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients.
[c]CGI-I scores: 3 = very much improved; 2 = much improved; 1 = minimally improved; 0 = no change; –1 = minimally worse; –2 = much worse; –3 = very much worse.
[d]Mirtazapine daily dose was increased to 30 mg to decrease sedation.
[e]Discontinuation of mirtazapine due to side effects.

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synaptic and postsynaptic α_2-adrenoceptors. The possible synergy of these 2 mechanisms—increasing synaptic substrate and blocking negative feedback sites—may be responsible for the rapid and robust response observed in our refractory depressed patients who improved when mirtazapine was added to their regimens.

In considering which patient features were most often associated with positive response to mirtazapine, no clear-cut pattern emerged. Those whose primary antidepressant regimens were SSRIs fared about the same as those who were being treated with venlafaxine or combination antidepressants that already had some noradrenergic activity. Depressed patients with a variety of primary DSM-IV mood disorder diagnoses responded equally well to mirtazapine augmentation.

The patients participating in this study were defined as treatment refractory based on failure to achieve adequate response after a minimum of 4 weeks on the maximum tolerated dose of a primary antidepressant. The duration criterion was chosen, in part, to reflect current clinical practice, as monthly medication evaluations often present the typical point of assessment and medication change in the outpatient treatment of depression. Several of the patients in this series would not have met more stringent criteria for treatment refractoriness, but most had been taking their primary antidepressant medications for prolonged periods of time and had failed multiple prior antidepressant trials. Although a statistical analysis of the relationship between response and degree of treatment refractoriness is not possible with these preliminary data, our results did not suggest a pattern of association between those 2 variables.

While the addition of mirtazapine appeared to confer a dramatic antidepressant response in some of the patients we studied, certain side effects were prominent and resulted in discontinuation in several cases, despite clinical improvement. Weight gain was the most common side effect, occurring in 5 (25%) of the patients, none of whom were concurrently taking desipramine. Sedation was described by 4 patients (20%) from our sample. Weight gain and sedation are side effects typically produced by blockade of the histamine H_1 receptors. Reviews of the pharmacologic profile of mirtazapine[14,15] suggest that the drug has powerful antihistaminic actions at lower doses, whereas the drug's ability to work via α_2-adrenoceptor blockade occurs in the higher (15–45 mg/day) dose range.[15] Analyses of adverse events data collected in placebo-controlled clinical trials of mirtazapine reflect a substantial difference in the

prevalence of somnolence and weight gain, depending on whether the mirtazapine dose was higher or lower than 15 mg/day.[16] Among patients treated with low-dose mirtazapine, 55% and 15% reported somnolence and weight gain, respectively. In the group receiving higher doses, only 15% reported somnolence and 1% reported weight gain.

With these recent findings in mind, we used higher mirtazapine doses (30 mg/day) for augmentation in several of our patients who experienced marked sedation. Our limited experience with the drug as an augmentation agent anecdotally supported the notion that antihistamine-like side effects were more prominent with mirtazapine, 15 mg/day, and often abated when the dose was increased to 30 mg/day. This clinically provocative finding has encouraged us to titrate mirtazapine more liberally when weight gain or sedation is present.

The present preliminary findings will require replication under randomized, placebo-controlled conditions. Future trials also will be needed to address the question of optimal dose for mirtazapine augmentation and to determine whether the promising responses of the type we describe here are sustained beyond a 4-week follow-up period.

Drug names: bupropion (Wellbutrin), clonazepam (Klonopin), desipramine (Norpramin and others), fluoxetine (Prozac), levothyroxine (Synthroid and others), lorazepam (Ativan and others), mirtazapine (Remeron), paroxetine (Paxil), perphenazine (Trilafon), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor), yohimbine (Yocon and others).

REFERENCES

1. Anderson I, Tomenson B. The efficacy of selective serotonin re-uptake inhibitors in depression: a meta-analysis of studies against tricyclic antidepressants. J Psychopharmacol (Oxf) 1994;8:238–249
2. Stahl SM. Are two antidepressant mechanisms better than one? [BRAINSTORMS] J Clin Psychiatry 1997;58:339–340
3. Thomas D, Nutt D, Holman R. Effects of acute and chronic electroconvulsive shock on noradrenaline release in the rat hippocampus and frontal cortex. Br J Pharmacol 1992;106:430–434
4. Nelson JC, Mazure CM, Bowers MB, et al. A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. Arch Gen Psychiatry 1991;48:303–307
5. Nierenberg A, Feighner J, Rudolph R, et al. Venlafaxine for treatment-resistant unipolar depression. J Clin Psychopharmacol 1994;14:419–423
6. de Montigny C, Haddjeri N, Mongeau P. The effects of mirtazapine on interactions between central noradrenergic and serotonergic systems. CNS Drugs 1995;4(suppl 1):13–17
7. Cappiello A, McDougle C, Malison R, et al. Yohimbine augmentation of fluvoxamine in refractory depression: a single-blind study. Biol Psychiatry 1995;38:765–767
8. Pollack M, Hammerness P. Adjunctive yohimbine for treatment in refractory depression. Biol Psychiatry 1993;33:220–221
9. Sachs GS, Pollack MH, Brotman AW, et al. Enhancement of ECT benefit by yohimbine. J Clin Psychiatry 1986;47:508–510
10. deBoer T, Ruigt G. The selective alpha 2-adrenoreceptor antagonist mirtazapine (ORG 3770) enhances noradrenergic and 5-HT_{1A}-mediated serotonergic neurotransmission. CNS Drugs 1995;4(suppl 1):29–38
11. Summel G, Dopheide J, Stahl S. Mirtazapine: an antidepressant with noradrenergic and specific serotonergic effects. Pharmacotherapy 1997; 17:10–21
12. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
13. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
14. deBoer T. The pharmacologic profile of mirtazapine. J Clin Psychiatry 1996;57(suppl 4):19–25
15. Davies R, Wilde M. Mirtazapine: a review of its pharmacology and therapeutic potential in the management of major depression. CNS Drugs 1996;5:389–402
16. Stahl SM, Kremer C, Pinder R. Tolerability of mirtazapine used in high or low initial dose. In: New Research Program and Abstracts of the 150th Annual Meeting of the American Psychiatric Association; May 20, 1997; San Diego, Calif. Abstract NR242:133

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