Mirtazapine in Major Depression With Comorbid Generalized Anxiety Disorder

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Background: A high proportion of patients with generalized anxiety disorder (GAD) have comorbid depressive illness. The presence of anxiety in depression has significant prognostic implications. Because of mirtazapine's early anxiolytic effects, the present study was undertaken as a preliminary investigation in patients with a diagnosis of major depression with comorbid GAD.

Method: Mirtazapine was administered to 10 patients with DSM-IV major depressive disorder and comorbid GAD in an 8-week open-label study. Mirtazapine was increased from an initial daily dose of 15 mg to a maximum daily dose of 45 mg.

Results: Patients were found to have significant reductions in Hamilton Rating Scale for Depression scores, Hamilton Rating Scale for Anxiety scores, and Beck Depression Inventory scores, with improvement noted after the first week of therapy and continuing improvement over the 8 weeks of study.

Conclusion: These positive preliminary findings support the further investigation of mirtazapine's potential value as a treatment for generalized anxiety disorder in addition to its established efficacy as an antidepressant drug.

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Anxiety symptoms and disorders frequently coexist in patients with major depression. As many as one half of patients presenting with major depression have a concomitant anxiety disorder, most commonly generalized anxiety disorder (GAD), panic disorder, or social phobia.[1] The presence of anxiety symptoms or disorders has been found to be associated with increased severity and poorer outcomes of depression, including an increased risk of suicide.[2] Several antidepressants have been found to be effective for GAD and major depression.[3] Few studies have been conducted of antidepressants in treating GAD alone, but interest in their use is increasing as alternatives to benzodiazepines are sought.[4–6]

Mirtazapine is an effective antidepressant with pronounced early anxiolytic effects in patients with major depression.[7] Mirtazapine enhances both noradrenergic and serotonergic transmission and demonstrates postsynaptic blockade of both serotonin-2 (5-HT_2) and serotonin-3 (5-HT_3) receptors, which may limit side effects associated with nonselective 5-HT activation and also contribute to the anxiolytic and sleep-improving properties of the drug.[8] In a randomized double-blind trial in nondepressed patients with a primary anxiety disorder, mirtazapine, 15 to 25 mg/day, showed a continuously increasing anxiolytic effect over 28 days that was statistically superior to the effect of placebo.[9]

The present study was undertaken as a preliminary investigation of whether mirtazapine, because of its early anxiolytic effects, may successfully treat patients with the diagnosis of major depression and comorbid GAD.

METHOD

Ten patients (4 men, 6 women), mean ± SD age of 42.4 ± 9.5 years (range, 33–65 years), meeting DSM-IV criteria for both major depressive disorder and GAD, were prescribed mirtazapine for 8 weeks in an open-label study. The diagnosis of GAD was based on the presence of multiple complaints indicative of GAD, such as delayed sleep onset (i.e., initial insomnia), muscle tension or feeling "keyed up" or "edgy," and/or excessive worry. Patients received mirtazapine, 15 mg, once daily at bedtime for 1 week, 30 mg/day for 3 weeks, and then 45 mg/day for 4 weeks. Compliance with medication intake was assessed by physician inquiry and pill count.

Patients were selected by response to an advertisement. The exclusion criteria were women who were pregnant, nursing, or using inadequate contraception; use of any other concomitant psychotropic medication; presence of any other Axis I diagnosis; patients who met DSM-IV criteria for abuse or dependence on any drug including al-

Table 1. Rating Scale Results (mean ± SD)[a]

		Week			
Scale	Baseline	1	2	4	8
HAM-D	25.8 ± 4.4	15.6 ± 5.6	14.8 ± 5.8*	11.2 ± 6.1*	7.9 ± 6.0*
HAM-A	26.6 ± 7.6	17.6 ± 7.3†	17.8 ± 7.6†	13.5 ± 8.5*	8.5 ± 7.8*
BDI	32.7 ± 9.9	24.0 ± 11.2†	20.2 ± 14.2*	17.3 ± 13.8*	13.1 ± 12.4*
Q-LES-Q	185.7 ± 66.4	...	...	...	242.2 ± 89.6

[a]Abbreviations: BDI = Beck Depression Inventory, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.
*p ≤ .001 (paired t test).
† p ≤ .01 (paired t test).

Table 2. HAM-D Factor Improvement

Factor	Baseline	8 Weeks
Factor VI: sleep disturbance	4.3 ± 1.2	1.3 ± 1.6*
Factor III: cognitive disturbance	5.2 ± 2.6	0.9 ± 1.3*
Factor I: anxiety/somatization	9.2 ± 3.6	2.7 ± 2.3*
Factor V: retardation	6.7 ± 2.9	2.3 ± 2.3†

*p ≤ .001 (paired t test).
†p ≤ .01 (paired t test).

cohol within 6 months; patients who would represent a serious suicide risk during the course of the study; patients with medical contraindications to therapy with antidepressants based on medical history; patients with a known allergy or hypersensitivity to antidepressants; and patients judged by the investigator to be unable or unlikely to follow the study protocol.

Patients in the study discontinued all previous medication, and no patient had a clear pattern of treatment resistance or nonresponse. Four patients had never used an antidepressant prior to the study, 4 patients had shown a minimal response to an antidepressant for a prior depressive episode, and 2 had discontinued their antidepressant owing to adverse effects. The study was approved by the Institutional Review Board of the University of Miami School of Medicine, and written informed consent was obtained from all patients before entering the study.

Assessments were carried out at the baseline visit and after 1, 2, 4, and 8 weeks of therapy. The screening visit included psychiatric diagnostic interview, medical history, and administration of rating instruments: Hamilton Rating Scale for Anxiety (HAM-A),[10] Hamilton Rating Scale for Depression (HAM-D),[11] and Beck Depression Inventory (BDI).[12] Each of these rating instruments was repeated at the baseline visit and after weeks 1, 2, 4, and 8 of therapy. In addition, at the beginning and end of the study, patients completed the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[13] The Q-LES-Q is a 93-item self-report measure that includes categories of physical health, subjective feelings, leisure time activities, social relationships, general activities, and, when applicable, work, household duties, and school/course work. Adverse effects were evaluated by direct patient interview.

Blood mirtazapine levels were obtained at the end of the study. The mirtazapine assay was done by the gas chromatographic method of Paanakker and Van Hall[14] using nitrogen detection. The statistical analyses used to assess significance of change in HAM-D, HAM-A, and BDI scores from baseline through week 8 of treatment included the paired t test and Pearson correlation test. All p values were deemed statistically significant at p ≤ .05.

RESULTS

There was significant improvement in scores on all rating scales used, with improvement noted after the first week of therapy and continuing to improve over the 8 weeks of study. Table 1 presents aggregate data on the rating scales. Four of 10 patients had a 50% reduction in HAM-D score from baseline after 1 week of therapy, 7 of 10 patients after 4 weeks, and 8 of 10 patients after 8 weeks of therapy. Table 2 lists the 4 HAM-D factors showing greatest improvement during the study. Three of 10 patients had a 50% reduction in BDI score after 1 week, 5 patients after 4 weeks, and 6 patients after 8 weeks of therapy. Three of 10 patients had a 50% reduction in HAM-A score from baseline after 1 week of therapy, 5 patients after 4 weeks, and 8 patients after 8 weeks of mirtazapine therapy. Furthermore, there was an improvement noted in the self-rating scores on the Q-LES-Q from a mean total of 185.7 (baseline) to 242.2 (week 8).

The most common adverse effect observed in the study was sedation in 4 patients, mostly occurring early in the study. Blurred vision was mentioned by 2 patients, while dry mouth, decreased memory, headache, and shortness of breath were mentioned by 1 patient each. Two patients experienced a slight increase in weight of 1 lb (0.45 kg) and 1.1 lb (0.5 kg), respectively (one of these was an underweight male). Three patients had no adverse effects over the 8 weeks, and no patient discontinued treatment owing to adverse effects.

Problems in shipment allowed only 7 of the 10 patients' plasma samples to be assayed for mirtazapine levels. Plasma concentrations of mirtazapine varied from 14 to 63 ng/mL. The change in HAM-A scores showed a trend toward improvement with increasing plasma values

($r = 0.73$, $p = .06$). The 3 patients with the higher plasma levels had much greater improvement in both HAM-D and HAM-A scores than the 4 patients with the lower plasma levels (mean HAM-D improvement of 23 vs. 9.75 [$p < .01$]; mean HAM-A improvement of 20 vs. 9.75 [$p < .01$]).

DISCUSSION

In this open trial, mirtazapine was shown to reduce symptoms of both anxiety and depression in patients meeting criteria for major depression and generalized anxiety disorder. The improvement appeared to begin as early as 1 week after initiation of therapy, and symptoms of anxiety and depression continued to improve over the 8 weeks of therapy. While it is not surprising to observe the improvement in the HAM-D sleep and anxiety factors with mirtazapine, on the basis of its known mechanism, it is of interest that mirtazapine's potential to cause somnolence seemed not to have any negative effect on the improvements noted in the HAM-D cognitive disturbance and retardation factors. In addition, there were no patient dropouts in this study, and mirtazapine was well-tolerated without evidence of SSRI-type adverse events such as sexual dysfunction, insomnia, gastrointestinal distress, diarrhea, or agitation. As an open-label, uncontrolled trial, no conclusive claims can be made regarding mirtazapine's efficacy for patients with coexisting major depression and GAD. However, symptoms of major depression and GAD were statistically significantly reduced in 8 of 10 patients. Although patients showed improvement overall in quality of life, definitive clinical interpretation of the magnitude of improvement is difficult in a pilot study. The results of this study support further investigation of mirtazapine's use in this population of patients.

Drug name: mirtazapine (Remeron).

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