A Meta-Analysis of Eight Randomized, Double-Blind, Controlled Clinical Trials of Mirtazapine for the Treatment of Patients With Major Depression and Symptoms of Anxiety

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Background: Patients diagnosed with major depression and prominent symptoms of anxiety often have a poor prognosis for recovery. A meta-analysis was performed to assess the efficacy of mirtazapine in comparison with placebo and amitriptyline for the relief of anxiety/agitation or anxiety/somatization in patients with major depressive illness.

Method: A meta-analysis of eight randomized, double-blind, placebo-controlled clinical trials was conducted for 161 mirtazapine-treated and 132 placebo-treated patients with a DSM-III diagnosis of major depression, baseline Hamilton Rating Scale for Depression (HAM-D) scores ≥ 18, and a baseline score ≥ 6 for the sum of HAM-D items 9, 10, and 11 (anxiety/agitation). Four of the clinical trials included an amitriptyline control group (N = 92).

Results: Mirtazapine-treated patients demonstrated a statistically significant ($p \leq .05$) reduction in the sum of HAM-D items 9, 10, and 11 (anxiety/agitation) compared with placebo-treated patients at Weeks 1, 2, 4, and 6 and at the endpoint. There was no statistically significant difference between the mirtazapine- and amitriptyline-treated patients at Weeks 1, 3, 4, 5, and 6 and at the endpoint. Similar results were found for the analysis of the mean of HAM-D items 10, 11, 12, 13, 15, 17 (anxiety/somatization or HAM-D Factor Score I) using all treated patients with a post-baseline evaluation in all 8 studies. Mirtazapine-treated patients demonstrated a statistically significant ($p \leq .03$) greater reduction at Weeks 1–6 compared with placebo, and improvement in the mirtazapine group was comparable to improvement in the amitriptyline group at Weeks 1–6.

Conclusion: In this meta-analysis of eight randomized, double-blind, controlled clinical trials, mirtazapine was found to be superior to placebo and comparable to amitriptyline for the treatment of patients with major depression with symptoms of anxiety/agitation or anxiety/somatization.

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Anxiety frequently coexists with depression, and it is a clinical challenge to distinguish between the two diagnoses.[1,2] Approximately 50% to 70% of patients diagnosed with depression have moderate anxiety while 20% to 25% have severe levels of anxiety. More than 50% of patients with panic attacks have had at least one major depressive episode.[3,4] Anxiety associated with major depression may be expressed in several forms including severe agitation, psychic anxiety, and panic disorders.[4] The prognosis for recovery from major depression may be incomplete for patients who have severe existing global anxiety subcomponents.[5] A prospective study of 25 suicides compared with 929 major affective disorder patients who made no suicide attempts indicates that those patients with severe psychic anxiety, panic attacks, and agitation are at a higher risk for suicide within days to months after initiating treatment.[6,7] A review of the biological factors of suicide indicate that hypophyseal-pituitary-adrenal activation can lead to severe anxiety and agitation, which are markers in suicide, especially in those patients with depression, possibly through the mechanisms modulated by corticotropin-releasing factor (CRF).[8]

The antidepressants currently used to treat major depression with anxiety subcomponents differ in their effects upon the various neurotransmitter systems, producing both clinically beneficial and adverse effects.[9,10] Adverse effects such as akathisia, restlessness, agitation, jitteriness, and insomnia have been reported in those patients taking tertiary amines (e.g., imipramine), secondary amines, (e.g., desipramine), trazodone, phenelzine, or serotonin selective reuptake inhibitors (SSRIs).[11,12] Symptoms most often occurred within 1 to 2 weeks after starting the drug or a dose increase and were often accompanied by suicidal thoughts.

Mirtazapine is the first among a new class of antidepressants known as NaSSAs (noradrenergic and specific

serotonergic antidepressants), whose efficacy and effectiveness has been established in a series of active- and/or placebo-controlled clinical trials in the United States and Europe.[13] Mirtazapine increases noradrenergic and serotonergic neurotransmission by blocking both central α_2-adrenergic autoreceptors and α_2-serotonergic heteroreceptors[14] and selectively antagonizes postsynaptic serotonin 5-HT_2 and 5-HT_3 receptors, which allows increased serotonin release and 5-HT_1-mediated neurotransmission.[15] The 5-HT_2 and 5-HT_3 blockade may account for mirtazapine's low incidence of SSRI-related adverse effects, such as anxiety, headache, insomnia, nausea, and sexual dysfunction.[13,16] Mirtazapine also has little or no affinity for dopaminergic, cholinergic, or α_1 receptors and moderate affinity for histaminergic (H_1) receptors.[14,15]

The rapid improvement in the symptoms of anxiety/agitation could have important clinical implications when choosing antidepressant therapy for patients with significant anxiety symptoms. Therefore, a principle objective of the meta-analysis was to examine the response to selected items on the HAM-D scale, such as agitation (HAM-D item 9) and anxiety (HAM-D items 10 and 11) that might be expected to show rapid or marked improvement based upon the pharmacology of mirtazapine. Anxiety/somatization is a broad factor, which includes symptoms of anxiety and other HAM-D items that might not necessarily show a marked or rapid improvement based on pharmacodynamic considerations. However, a meta-analysis of anxiety/somatization was included because somatic symptoms of anxiety are also evident in many depressed patients.

METHOD

Patients

A meta-analysis was conducted to evaluate the effect of mirtazapine on the symptoms of anxiety/agitation or anxiety/somatization (HAM-D Factor Score I) associated with depression. In the worldwide clinical trials, the efficacy of mirtazapine was based on 11 controlled studies overall, but only the data from 8 randomized, double-blind, controlled studies conducted in the United States were selected for the meta-analysis. Only data from the U.S. clinical trials were used in the meta-analysis because no other psychotropic medications were allowed in these trials. This was not necessarily true for non-U.S. studies, in which the concomitant use of benzodiazepines during the first 2 weeks of treatment might confound an evaluation of the response to mirtazapine during the early portion of the clinical trials. Five of the eight trials are published, four with active- and placebo-control groups and one with a placebo-control group.[17–21]

All eight studies included placebo and four of the eight studies included amitriptyline. These randomized, double-blind, placebo-controlled clinical trials included moderately to severely depressed patients with total baseline Hamilton Rating Scale for Depression[22] (HAM-D) scores equal to or greater than 18 for the first 17 items on the 21-item HAM-D and a score of 6 or more for the HAM-D anxiety/agitation factor. The 17-item HAM-D score was used since the four additional items (diurnal variation, depersonalization/derealization, paranoia, and obsessive-compulsive symptoms) are not quintessential features of depressive illness. The HAM-D anxiety/agitation factor is defined as the sum of items 9 (agitation), 10 (anxiety, psychic), and 11 (anxiety, somatic). The rationale for the threshold is that a score of 6 represents moderate anxiety/agitation, based on a maximum score of 12 and a minimum score of 0 for the sum of HAM-D items 9, 10, and 11. The HAM-D anxiety/somatization factor is defined as the mean of items 10 (anxiety, psychic), 11 (anxiety, somatic), 12 (somatic symptoms, gastrointestinal), 13 (somatic symptoms, general), 15 (hypochondriasis), and 17 (loss of insight).[23]

All studies were similar in design, inclusion/exclusion criteria, response variables, assessment schedules, and doses. Exclusion criteria included a history of schizophrenia or other psychotic disorder, atypical depression, drug or alcohol abuse, attempted drug overdose, attempted suicide, or clinically significant medical illness. Concomitant use of other psychotropic medication was prohibited and none of the patients had received electroconvulsive therapy in the previous 3 months. Women of childbearing potential were included if they were adequately protected against pregnancy. Breast-feeding mothers and those within 6 months postpartum were excluded from the studies.

Medications and Dosages

Seven studies were randomized, double-blind, flexible-dose comparisons of 6 weeks' duration. One study was a randomized, double-blind, fixed–dose range study. Doses were tailored to individual patient needs and titrated up or down based on patient response. The dosage was decreased only if the patient was experiencing intolerable adverse reactions. Doses of mirtazapine ranged from 5 to 35 mg per day in the flexible-dose studies and 5, 15, 30, and 60 mg per day in the fixed-dose studies. The doses used for amitriptyline ranged from 40 to 280 mg per day and 1 to 7 capsules or tablets per day for identically appearing placebo.

Statistical Analysis

General linear model (GLM) analyses of raw scores and rank-transformed scores (henceforth, called GLM and rank analysis, respectively) were performed on those efficacy-evaluable patients with a sum of ≥ 6 of a possible score of 12 for the HAM-D anxiety/agitation factor. The HAM-D anxiety/agitation factor ratings were collected at baseline, weekly throughout the study, and at endpoint.

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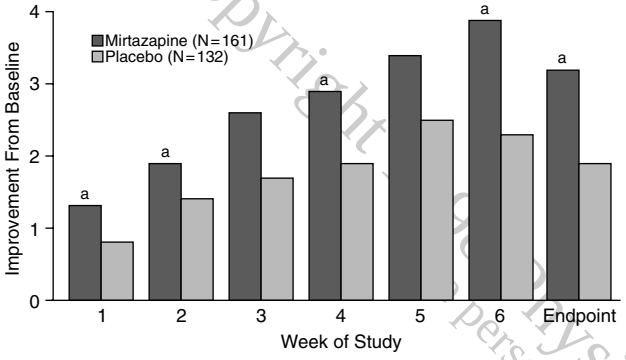
Table 1. Patient Demographics*

Characteristic	Mirtazapine (N = 161)	Amitriptyline (N = 92)	Placebo (N = 132)
Age (y)			
Range	18–80	18–93	18–85
Mean	44	42	44
Sex			
Male (%)	47	43	40
Female (%)	53	57	61

*N = number of patients who met the criteria for high levels of anxiety/agitation at the baseline visit.

Figure 1. Mean Improvement From Baseline Anxiety/ Agitation Factor in the Mirtazapine vs. Placebo Groups*

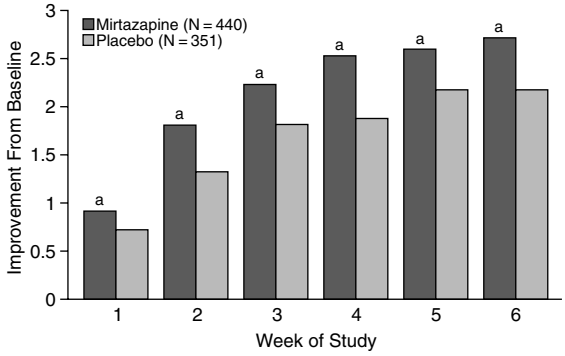


*Anxiety/agitation factor = sum of HAM-D items 9, 10, and 11.
[a]Statistically significant improvement in the mirtazapine group compared with the placebo group at Weeks 1, 2, 4, and 6 and at endpoint ($p \leq .05$). ANOVA rank analysis.

Separate rank and GLM analyses were performed on the intent-to-treat group, which included all patients who had received at least one dose of the study medication and had at least one postbaseline efficacy evaluation for the HAM-D anxiety/somatization factor. Weekly observed-case and endpoint analyses were performed for the anxiety/agitation factor, while last-observation-carried-forward analyses were performed for the HAM-D anxiety/somatization factor weekly throughout the studies. Although the results of the anxiety/somatization statistical analysis were calculated as changes from the means of items 10, 11, 12, 13, 15, and 17, the results are presented as the sums of these items (denoted ∑ HAM-D Factor Score I) for the purpose of consistency with the presentation of anxiety/agitation.

The rank analysis performed was an analysis of variance (ANOVA) on the change of baseline score from rank-transformed data, with ranking done over all observations. The statistical model used included terms for study, treatment group, and the interaction of study and treatment group. The GLM analysis performed was an ANOVA on the change from baseline raw data. The statistical model used included terms for study, treatment group, and the interaction of study and treatment group. The rank analysis was the primary method of evaluating

Figure 2. Mean Improvement From Baseline Anxiety/ Somatization Factor in the Mirtazapine vs. Placebo Groups*



*Anxiety/somatization factor = sum of HAM-D items 10, 11, 12, 13, 15, and 17.
[a]Statistically significant improvement in the mirtazapine group compared with the placebo group at Weeks 1–6 ($p \leq .03$). ANOVA rank analysis.

data and presenting the p value. The GLM analysis was used to support rank analysis findings. Statistical significance was declared at the $p \leq .05$ level.

RESULTS

Age and sex of each treatment group are summarized in Table 1. Women comprised 57% and men 43% of the study population. The mean patient age was 43, with a range of 18 to 93 years of age.

Mirtazapine Versus Placebo

Approximately 41% (161/390) of mirtazapine-treated patients and 41% (132/321) of placebo-treated patients met the criteria for high baseline levels of anxiety. Baseline HAM-D scores for anxiety/agitation were 6.8 ± 1.0 for the mirtazapine-treated patients and 6.7 ± 1.0 for the placebo-treated patients. The mirtazapine-treated patients experienced a significant ($p \leq .05$) reduction in the symptoms of anxiety at Weeks 1, 2, 4, and 6 and at the endpoint compared with placebo. At the endpoint, the magnitude of change from baseline was $3.2 \pm .02$ for the mirtazapine-treated patients as compared to $1.9 \pm .02$ for the placebo-treated patients (Figure 1).

Similar results were noted in the meta-analysis of the HAM-D anxiety/somatization factor (Figure 2). The mirtazapine-treated patients (N = 440) demonstrated a significant ($p \leq .03$) reduction in anxiety/somatization symptoms at Weeks 1 through 6 as compared with the placebo-treated patients (N = 351). At the end of the study, the magnitude of change from baseline was $0.45 \pm .02$ (∑ HAM-D Factor Score I = 2.7) points for the mirtazapine-treated patients compared with $0.36 \pm .02$ (∑ HAM-D Factor Score I = 2.2) points for the placebo-treated patients.

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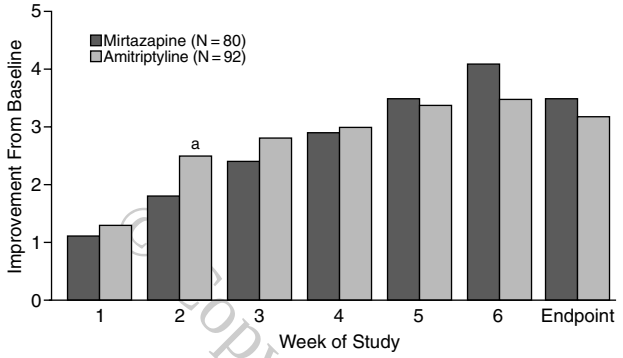
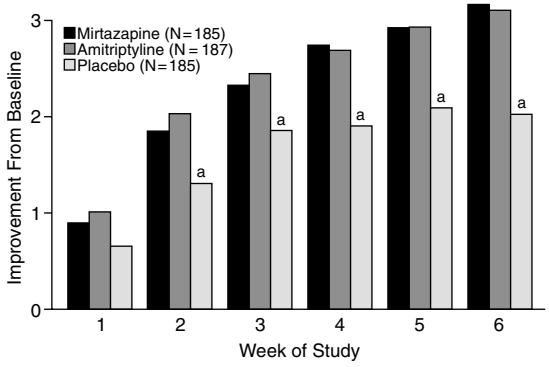
Figure 3. Mean Improvement From Baseline Anxiety/ Agitation Factor in the Mirtazapine vs. Amitriptyline Groups*



*Anxiety/agitation factor = sum of HAM-D items 9, 10, and 11.
[a]Statistically significant improvement in the amitriptyline group compared with the mirtazapine group at Week 2 ($p \leq .05$). ANOVA rank analysis.

Figure 4. Mean Improvement From Baseline Anxiety/ Somatization Factor in the Mirtazapine vs. Amitriptyline Groups*



*Anxiety/somatization factor = sum of HAM-D items 10, 11, 12, 13, 15, and 17.
[a]Statistically significant improvement in the mirtazapine and amitriptyline groups compared with the placebo group at Weeks 2–6 ($p \leq .05$). No statistically significant difference was found between the two active treatment groups. ANOVA rank analysis.

Mirtazapine Versus Amitriptyline

Approximately 46% (80/174) mirtazapine-treated patients and 54% (92/170) amitriptyline-treated patients met the criteria for high baseline levels of anxiety. Baseline HAM-D anxiety/agitation scores were 7.0 ± 1.1 for the mirtazapine-treated patients and 6.9 ± 0.9 for the amitriptyline-treated patients. There was a statistically significant difference between mirtazapine and amitriptyline in reducing the sum of anxiety/agitation only at Week 2 (Figure3). At the study endpoint, the mean reduction from baseline was 3.5 ± 0.3 points for the mirtazapine-treated patients and 3.2 ± 0.2 points for the amitriptyline-treated patients.

Similar results were noted for the meta-analysis of the HAM-D anxiety/somatization factor (Figure 4). There were no statistically significant differences between mirtazapine-treated (N = 185) and amitriptyline-treated patients (N = 187) during Weeks 1 through 6. The mean reduction from baseline was $0.53 \pm .04$ ($\sum$ HAM-D Factor Score I = 3.18) points for the mirtazapine-treated patients and $0.52 \pm .04$ ($\sum$ HAM-D Factor Score I = 3.12) points for the amitriptyline-treated patients. Both active treatment groups showed a significant ($p < .05$) reduction in the symptoms of anxiety/somatization compared with placebo, beginning at Week 2.

DISCUSSION

This meta-analysis of eight clinical trials showed that mirtazapine is superior to placebo for the treatment of patients with major depression and coexisting symptoms of anxiety/agitation or anxiety/somatization. The mirtazapine-treated patients demonstrated a significantly greater improvement in the anxiety/agitation symptoms compared with the placebo-treated patients, beginning at the first week of treatment and at the endpoint. The rapid response to symptoms of anxiety/agitation in depressive illness is particularly noteworthy since anxiety symptoms are very common in depressive illness.[9] Although the results are based on a retrospective analysis, the results have a pharmacologic basis since the characteristics of a particular antidepressant are often typified by the drug's pharmacodynamics. This meta-analysis suggests that the selective antagonization of postsynaptic 5-HT_2 and 5-HT_3 receptors may account for the early relief of anxiety symptoms as well as the low incidence (< 1%) of anxiety and/or agitation reported in clinical trials.[24] As a result, mirtazapine may decrease the need for anxiolytic or sedative/hypnotic polypharmacy. The meta-analysis of four of the eight trials that included an amitriptyline control group showed that mirtazapine and amitriptyline are comparable for the treatment of patients with depression and coexisting symptoms of anxiety/agitation or anxiety/somatization over the 6-week study period.

An awareness of the symptoms anxiety and/or agitation and a recognition of the clinical importance of prompt and effective treatment are necessary for a good prognosis for recovery from a major depressive episode. Effective therapy for the treatment of depressive illness must include a consideration of anxiety symptoms since anxiety has been estimated to be present in 96% of patients with depressive illness.[9] In addition, studies have indicated that depressed patients with significant anxiety may be at greater risk for suicide.[6,7] Early relief from this symptomatology might reduce the risk of suicide in patients with depression and significant anxiety. Relief from symptoms of anxiety/agitation or anxiety/somatization early in therapy also may help to improve patient compliance and improve the prognosis for recovery.

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Since the prognosis for recovery from a major depressive episode is less than optimal in patients with significant anxiety, effective treatment outcomes are of paramount importance. It is estimated that somatic symptoms of anxiety are evident in 86% of depressed patients.[9] The failure to effectively treat somatic complaints can create a significant degree of incremental health care utilization and diminish the ability to function. Drugs with serotonin reuptake inhibition may cause transient increases in anxious symptomatology when treatment is initiated and may be accompanied by jitteriness, insomnia, and diarrhea. In addition, anxiety and agitation can occur as a comorbid condition in the critical care patient[25] or as adjunctive symptoms in a variety of medical pathologies. A number of physical pathologies that often coexists with manifest anxiety symptoms include cardiovascular, endocrine, neurologic, metabolic, respiratory, and rheumatologic disorders and secretory tumors. Pharmacotherapeutic interventions include antidepressants with anxiolytic properties, adjunctive anxiolytic medication, or both modalities.[9,26] Adjunctive pharmacotherapy includes benzodiazepines, β-adrenergic blocking agents, buspirone, other anxiolytics (e.g., hydroxyzine) and clonidine. However, adjunctive therapy can be minimized by first employing an antidepressant that is effective in reducing the somatization of anxiety. These complaints include initial insomnia and symptoms associated with increased catecholamine activity as well as other multiple, diverse, changing somatic complaints.

In summary, mirtazapine is the first among a new class of antidepressants known as noradrenergic and specific serotonergic antidepressants which may offer a promising alternative to available antidepressants. Mirtazapine is superior to placebo and comparable to amitriptyline in treating patients with major depression and symptoms of anxiety/agitation or anxiety/somatization.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), buspirone (BuSpar), clonidine (Catapres), desipramine (Norpramin and others), fluoxetine (Prozac), hydroxyzine (Atarax and others), imipramine (Tofranil and others), mirtazapine (Remeron), paroxetine (Paxil), phenelzine (Nardil), trazodone (Desyrel and others), venlafaxine (Effexor).

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