DEPRESSION AND ANXIETY, VOLUME 7, SUPPLEMENT 1:7–10 (1998)

EFFICACY OF MIRTAZAPINE IN CLINICALLY RELEVANT SUBGROUPS OF DEPRESSED PATIENTS

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Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) with a novel mode of action that differs from other antidepressants that are currently available. Clinical trials have demonstrated it to have good antidepressant efficacy and excellent tolerability. Analysis of the results of placebo-controlled trials in moderately or severely depressed patients have shown mirtazapine to be effective in clinically important subgroups of depressed patients, particularly anxious patients, patients with sleep disturbance, retarded patients, and agitated patients. The efficacy and tolerability of mirtazapine are attributable to its pharmacological profile. It is likely that the overall antidepressant activity arises from its dual action, enhancing both noradrenergic and 5-HT$_1$ receptor-mediated serotonergic neurotransmission, while the anxiolytic and sleep-improving properties of mirtazapine are attributable to the specific blockade of 5-HT$_2$ and 5-HT$_3$ receptors. Depression and Anxiety, Volume 7, Supplement 1:7–10, 1998.

Key words: *efficacy; mirtazapine; depression; anxiety; sleep disturbance*

INTRODUCTION

Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA) with a novel mode of action that differs from other antidepressants that are currently available. Mirtazapine is an antagonist of presynaptic α_2-auto- and α_2-heteroceptors (de Boer, 1996), which results in an increased release of both noradrenaline and serotonin (5-HT), and enhancement of noradrenergic and 5-HT$_1$-mediated serotenergic neurotransmission (de Boer et al., 1994, 1995). In addition, mirtazapine potently blocks 5-HT$_2$ and 5-HT$_3$ receptors (de Boer, 1995).

Clinical trials have shown that mirtazapine is similar to tricyclic antidepressants in its overall efficacy (Kasper, 1995); in addition, it also demonstrated the relative absence of cholinergic, adrenergic, and serotonergic side effects, together with relative safety in overdose (Montgomery,1995).

EXPERIENCE WITH MIRTAZAPINE

A wide ranging clinical trial program in Europe and the United States has shown that mirtazapine has clear clinical benefits in a broad range of patients (Kasper, 1995). Both individual placebo-controlled studies of mirtazapine and a meta-analysis based on pooled data from these studies have demonstrated that mirtazapine is an effective antidepressant as assessed by the Hamilton Rating Scale for Depression (HAMD; Kasper, 1995). This clinical efficacy of mirtazapine in depression has also been corroborated by comparative studies with well established antidepressants such as amitriptyline, clomipramine, doxepin, tradozone, and fluoxetine (Kasper, 1995; Wheatly and Kremer, 1997).

This review will concentrate on the efficacy of mirtazapine versus placebo in clinically relevant subgroups of depressed patients, more particularly anxious patients, patients with sleep disturbance, retarded patients, and agitated patients.

A meta-analysis of pooled data was based on five randomized double-blind placebo-controlled studies of 5–6 week's duration (Kasper, 1995). Details of the dosage regimen of mirtazapine, duration of treatment and whether patients were outpatients or inpatients in each of the studies is shown in Table 1.

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Received for publication 3 November 1997; Accepted 19 November 1997

TABLE 1. Placebo-controlled studies[a]

Study site	Duration (weeks)	Dose (mg/day)	No. evaluable patients: Mirtazapine	No. evaluable patients: Placebo
USA	6 (OP)[b]	5–35	43	44
USA	6 (OP)	5–35	49	50
USA	6 (OP)	5–35	50	47
UK	5 (OP + IP)[c]	60–60	64	61
Finland	6 (OP + IP)	15–50	43	44
Total		23[d]	249	246

[a]*Adapted from Kasper (1995).*
[b]*OP, outpatients.*
[c]*IP, inpatients.*
[d]*Mean dose, including titration period.*

All patients were assessed as being moderately (17-item HAMD score 18–24) or severely depressed (17-item HAMD score –25) at baseline. A flexible dosage regimen was used to enable investigators to optimize daily doses in individual patients according to their overall response to treatment. All data were analyzed on an intent-to-treat basis, thus including all patients given at least one dose of blinded study medication, who had at least one postbaseline efficacy assessment. Both observed case and last observation carried forward (endpoint) analyses were performed on the scheduled assessment points.

The analysis of pooled data from the total of 495 evaluable patients (mirtazapine n = 249, placebo n = 246) showed that the change from baseline on the 17-item HAMD scores was statistically significantly larger with mirtazapine compared to placebo from week 1 onwards at all assessment times and at endpoint. At the end of the study, the magnitude of change from baseline was –14.0 ± 7.7 points in the mirtazapine patients and –10.0 ± 8.3 in the placebo patients (estimated treatment difference –4.0; 95% confidence interval: –6.0. –2.0; $P \leq 0.001$).

EFFICACY OF MIRTAZAPINE ON ANXIETY/ SLEEP DISTURBANCE IN DEPRESSED PATIENTS

To further investigate the efficacy of mirtazapine in some clinically relevant symptoms frequently seen in depressed patients, changes in the symptoms of anxiety and sleep disturbance in depression were examined, as assessed by the HAMD factors of anxiety/ somatization and sleep disturbance (Cleary and Guy, 1977), for the overall patient population (Fig. 1). The data show that the HAMD factors of anxiety/ somatization and sleep disturbance in patients treated with mirtazapine (n = 249) were significantly reduced ($P < 0.05$) compared with patients who received placebo (n = 246).

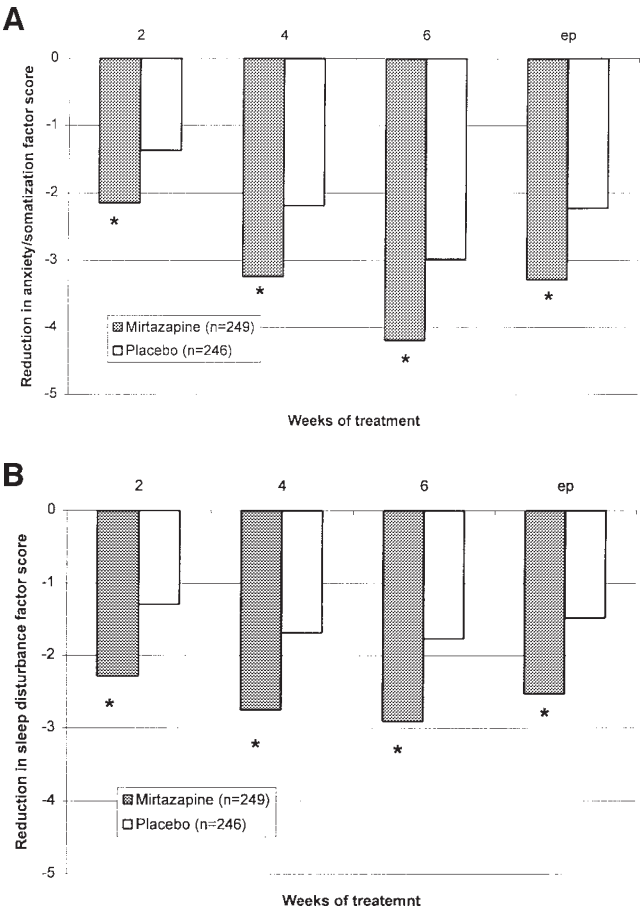

Figure 1. Reduction in HAMD factors of (*A*) anxiety/somatization, and (*B*) sleep disturbance in overall patient population (mirtazapine n = 249, placebo n = 246). *$P \leq 0.05$, mirtazapine vs. placebo.

EFFICACY OF MIRTAZAPINE IN PATIENTS WITH PROMINENT ANXIETY OR SLEEP DISTURBANCE AT BASELINE

Mirtazapine was highly effective, even in anxious patients and patients with sleep disturbance, who responded as well as the overall study population (Fig. 2). Analysis of the total 17-item HAMD scores in subgroups of 345 anxious patients (anxiety/somatization HAMD factor –7 at baseline) and 322 patients with sleep disturbance (sleep disturbance HAMD factor –4 at baseline) revealed that the total 17-item HAMD score was statistically significantly reduced with mirtazapine compared to placebo in both these subgroups (Figs. 3 and 4). In anxious patients, the change in total score from baseline to the endpoint was 12.5 ± 8.2 points for patients treated with mirtazapine, compared with 8.1 ± 8.4 points in the placebo patients (estimated treatment difference: –4.4; 95% confidence interval: –6.2; –2.7; $P = 0.000$). In patients with sleep disturbance, the change in total score from baseline to end-

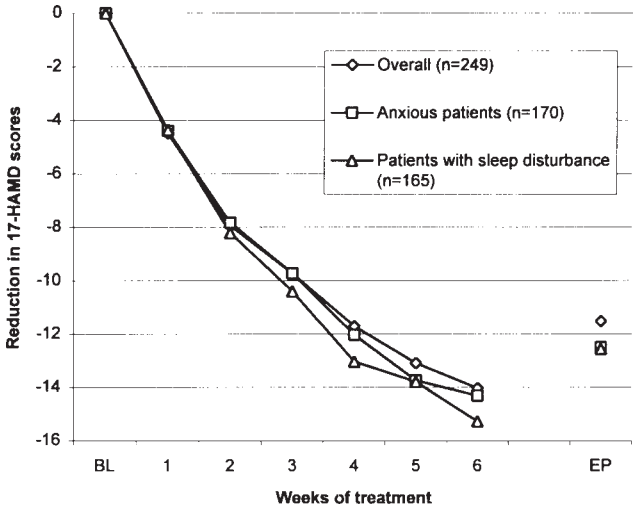

Figure 2. Reduction in total 17-HAMD scores in the overall population and in subgroups with high anxiety or sleep disturbance at baseline.

point was –12.6 ± 8.3 points for mirtazapine patients compared with –7.2 ± 8.9 points for placebo patients (estimated treatment difference: –4.9; 95% confidence interval: –6.7; –3.0; P = 0.000). Analysis of pooled data from five studies demonstrated a significant difference between placebo and mirtazapine at all time points ($P < 0.05$) and at the endpoint ($P < 0.0001$) in both these patient subgroups.

The anxiety/somatization subscore for the subgroup of anxious patients and the sleep disturbance subscore for the subgroup of patients with sleep disturbances were statistically significantly reduced in mirtazapine

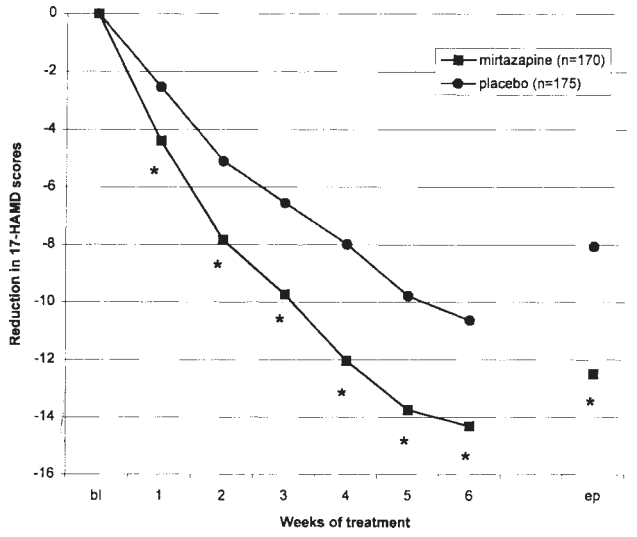

Figure 3. Reduction in total 17-HAMD scores in patients with an anxiety/somatization subscore of – 7 at baseline. *$P \leq 0.05$, mirtazapine vs. placebo.

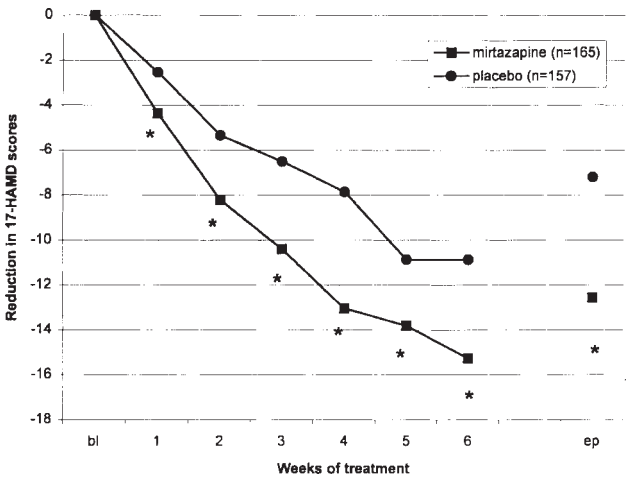

Figure 4. Reduction in total 17-HAMD scores in patients with a sleep disturbance subscore of –4 at baseline. *$P \leq 0.05$, mirtazapine vs. placebo.

patients compared with the subscores for placebo patients (Fig. 5). Overall results from two studies gave a change in anxiety/somatization subscore of –4.1 ± 3.0 points for mirtazapine patients compared with a change of –2.8 ± 2.9 points for placebo patients and a change in sleep disturbance subscore of –3.6 ± 1.8 points in mirtazapine patients compared with a change of –1.6 ± 2.2 points in placebo patients. Pooled results from five studies showed a significant difference between mirtazapine and placebo at all time points ($P < 0.05$) and at the endpoint ($P < 0.0001$) in these subscores for these two patient subgroups.

EFFICACY OF MIRTAZAPINE IN OTHER CLINICALLY IMPORTANT SUBGROUPS OF DEPRESSED PATIENTS

Statistically significant differences between mirtazapine and placebo were also seen in the total 17-item HAMD score in other clinically important subgroups of depressed patients, such as retarded or agitated patients (Fig. 6). The reduction in 17-item HAMD scores was as great in subgroups of patients with anxiety, sleep disturbance, agitation, or retardation as in the overall population of depressed patients.

CONCLUSIONS

The antidepressant efficacy of mirtazapine in moderately and severely depressed patients is clearly demonstrated in placebo-controlled studies. Mirtazapine was also effective in clinically important subgroups of depressed patients, particularly anxious patients, patients with sleep disturbance, retarded patients, and agitated patients, as demonstrated by a statistically significant reduction in total 17-item HAMD scores in patients on mirtazapine compared with placebo patients, irrespective of the patient population. Further-

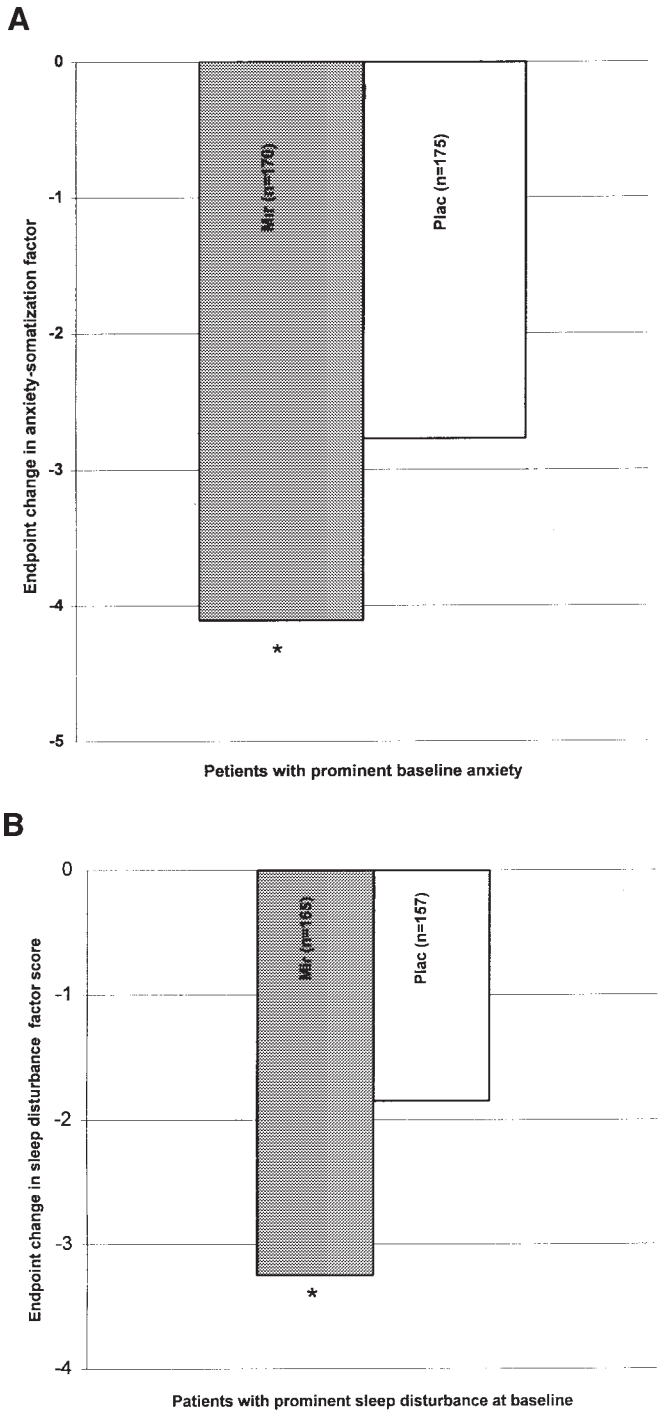

Figure 5. *A*: **Change from baseline to endpoint in anxiety/somatization subscore in patients with anxiety/somatization subscore of ≥7 at baseline.** *B*: **Change from baseline to endpoint in sleep disturbance subscore in patients with a sleep disturbance subscore of ≥4 at baseline. *$P \leq 0.05$, mirtazapine vs. placebo.**

more, sleep disturbances were significantly reduced in patients with high levels of sleep disturbance at baseline and anxiety symptoms in patients with high levels of anxiety at baseline.

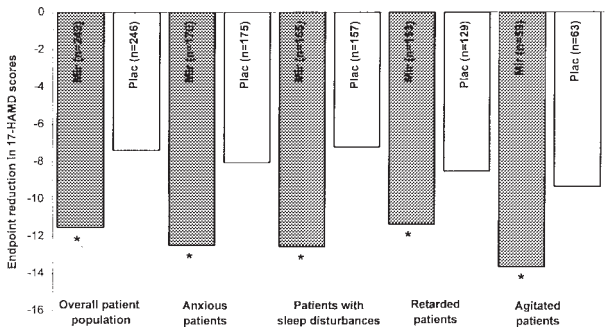

Figure 6. Reduction in total 17-HAMD scores in clinically important subgroups of depressed patients. *$P \leq 0.05$, mirtazapine vs. placebo.

Mirtazapine represents a new pharmacological concept in the treatment of depression. The overall antidepressant activity probably arises from the dual action, enhancing both noradrenergic and 5-HT_1-mediated serotonergic neurotransmission (de Boer, 1995). It is likely that the anxiolytic properties of mirtazapine are attributable to the specific blockade of 5-HT_2 and 5-HT_3 receptors, as well as indirect stimulation of presynaptic 5-HT_{1A} receptors (as are azapirone anxiolytics such as buspirone; de Boer et al., 1995; de Boer, 1995). The sleep-improving actions probably refelect a combination of 5-HT_2 and H1 blockade. These unique pharmacological properties of mirtazapine are also thought to be responsible for its excellent tolerability profile (Nutt, 1997).

Acknowledgments. With thanks to NV Organon, Oss, The Netherlands, for their support.

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