

# Mirtazapine: Clinical Overview

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There is currently available evidence that suggests that drugs combining 2 synergistic mechanisms of action (e.g., enhancement of both noradrenergic and serotonergic neurotransmission) may yield superior therapeutic efficacy compared with a single therapeutic mechanism of highly selective agents such as selective serotonin reuptake inhibitors (SSRIs). The differences in antidepressant efficacy favoring dual-acting drugs may exist in particular for 3 difficult-to-treat groups of patients: those with endogenous depression, those with severe depression, or hospitalized depressed patients. Mirtazapine differs from other new dual-acting antidepressants by not being a reuptake inhibitor. Its antidepressant activity may be related to a direct enhancement of noradrenergic neurotransmission by blockade of  $\alpha_2$ -autoreceptors. The rapid increase in serotonin (5-HT) synaptic levels by blockade of  $\alpha_2$ -heteroreceptors indirectly enhances 5-HT<sub>1A</sub>-mediated neurotransmission since 5-HT<sub>2</sub> and 5-HT<sub>3</sub> are blocked by mirtazapine. The antidepressant efficacy of mirtazapine was established in several placebo-controlled trials. Currently available evidence suggests that mirtazapine is effective in all levels of severity of depressive illness, as well as is in a broad range of symptoms associated with depression.

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Among the latest antidepressants appearing in the 1990s, some, such as reboxetine, have a single mode of action, while others, such as venlafaxine, milnacipran, and mirtazapine, have a dual mode of action. There is evidence that antidepressants with a dual action, e.g., affecting both the norepinephrine and serotonin systems, may be more effective under some circumstances than those that have only a single neurotransmitter action, such as the selective serotonin reuptake inhibitors (SSRIs).

## **SUPERIOR EFFICACY FOR DUAL-ACTING DRUGS?**

Tricyclic antidepressants (TCAs), some of which have a dual action, are traditionally the standard drug treatment against which all new antidepressants are compared. The efficacy of the SSRIs, which are highly selective, single-action agents, were compared with the TCAs in a meta-analysis of short-term trials by Anderson and Tomenson in 1994.<sup>1</sup> While there was no difference in efficacy when all of the studies were compared, the meta-analysis showed that SSRIs appeared to be less effective compared with TCAs in the treatment of hospitalized patients with depression and in those cases where the TCAs had a dual

mode of action, inhibiting the reuptake of both norepinephrine and serotonin.

An update of the 1994 meta-analysis included data from a further 48 studies, for a total of 10,496 patients from 101 studies.<sup>2</sup> The efficacy analysis included data from 25 studies on 1377 hospitalized depressed patients. The results of the comparison of efficacy of TCAs and SSRIs are shown in Figures 1 and 2. While the efficacy of SSRIs as a group appeared to be equal to that of the TCAs as a group, it was clear that amitriptyline was significantly superior to the SSRIs in efficacy by about 5% to 10%. The authors thought this might be related to amitriptyline's dual action of norepinephrine and serotonin reuptake inhibition. It may be that the superiority of these dual-acting TCAs gave the TCA group superior efficacy in hospitalized patients with depression.

These results were supported by a study that compared the SSRI fluoxetine with the TCA nortriptyline in hospitalized, depressed patients.<sup>3</sup> The intent-to-treat analysis of endpoint data showed 23% (5/22) were responders (Hamilton Rating Scale for Depression [HAM-D] score  $\leq 7$ ) for the SSRI versus 67% (28/42) for the TCA. Thus, differences in efficacy were found in favor of some TCAs, i.e., clomipramine and amitriptyline, compared with single-action SSRIs in severe depression or in major depression with melancholia,<sup>1-4</sup> particularly in hospitalized patients. It is important to note, however, that several studies do show SSRIs to be effective in treating more severely depressed patients.

## **NEW GENERATION ANTIDEPRESSANTS**

There is evidence that, unlike the SSRIs, the latest generation of antidepressants may have efficacy that is compa-

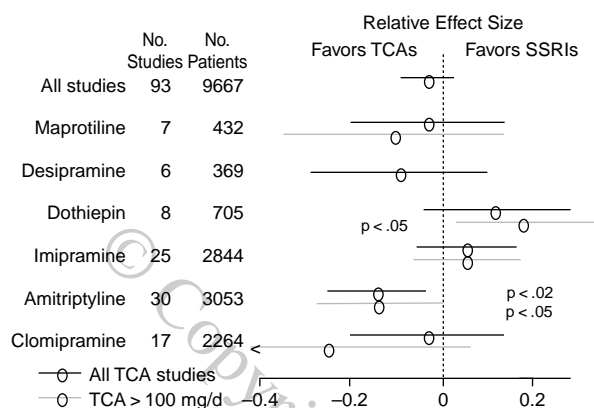
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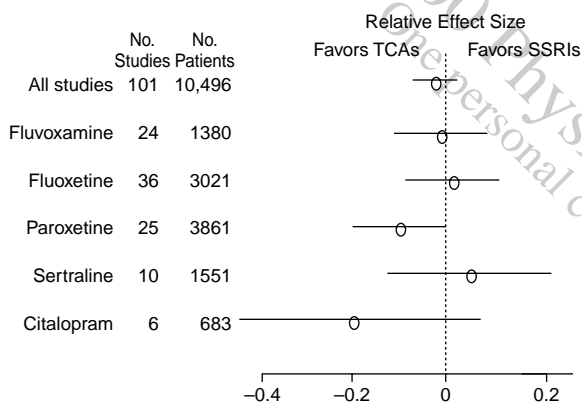
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**Figure 1. Efficacy of Individual Tricyclic Antidepressants (TCAs) vs. Selective Serotonin Reuptake Inhibitors (SSRIs)<sup>a</sup>**



<sup>a</sup>Data from reference 1.

**Figure 2. Efficacy of Individual SSRIs vs. TCAs<sup>a</sup>**



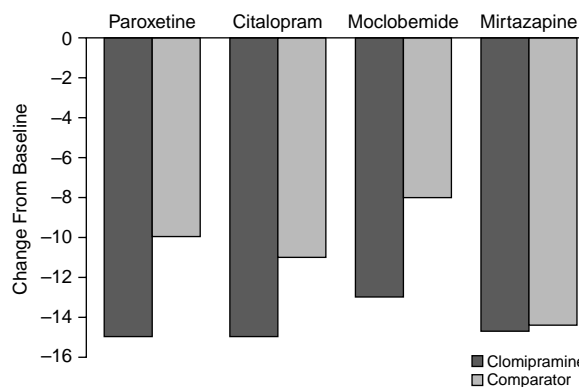
<sup>a</sup>Data from reference 1.

able to that of the TCAs for the treatment of severe depression. Comparisons of the magnitude of change at endpoint of HAM-D scores with various antidepressants (SSRIs, reversible monoamine oxidase inhibitors, and mirtazapine) versus that of the TCA clomipramine showed that only the latest dual-acting agent, mirtazapine, was associated with a change in HAM-D score comparable to that of clomipramine (Figure 3).<sup>5-8</sup>

**Venlafaxine**

Venlafaxine is a dual-action antidepressant that acts by blocking the reuptake of both norepinephrine and serotonin (5-HT). In the treatment of patients with major depression and melancholia, venlafaxine was seen to have significantly greater efficacy than placebo ( $p < .005$ ) from week 1 onward in a 6-week, double-blind, multicenter trial.<sup>9</sup> When compared with the SSRI fluoxetine in a 6-week, double-blind study, venlafaxine was associated

**Figure 3. Change in HAM-D Score at Endpoint Compared With Clomipramine<sup>a</sup>**



<sup>a</sup>Data from references 5-8. Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

**Table 1. An Overview of Clinical Trials Involving Mirtazapine<sup>a</sup>**

Reference Drug	Patient Population	No. of Patients	Overall Efficacy
Placebo	Inpatients and outpatients	258	Mirtazapine > placebo
Placebo	Outpatients or elderly	600	Mirtazapine > placebo
Amitriptyline			Mirtazapine = amitriptyline
Trazodone			Mirtazapine ≥ trazodone
Amitriptyline	Inpatients and outpatients or elderly	522	Mirtazapine = amitriptyline
Clomipramine	Inpatients	174	Mirtazapine = clomipramine
Doxepin	Inpatients and outpatients	163	Mirtazapine = doxepin
Trazodone	Inpatients	200	Mirtazapine > trazodone

<sup>a</sup>Data from reference 12. Symbols: >, significantly better than placebo; ≥, tended to be more effective than comparator; =, equal to comparator.

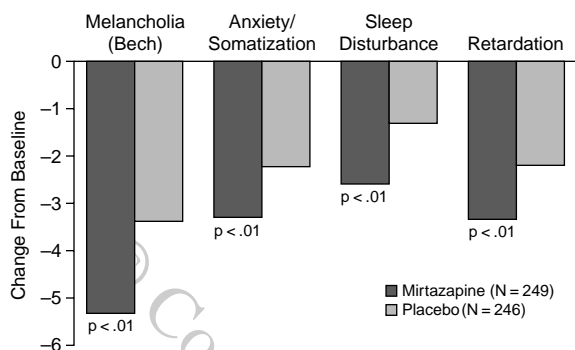
with significantly lower HAM-D and Montgomery-Asberg Depression Rating Scale (MADRS) scores than fluoxetine by 4 weeks in patients with major depression and melancholia ( $p < .005$ ).<sup>10</sup>

**Mirtazapine**

Mirtazapine has a dual mode of action that differs from that of venlafaxine and the SSRIs. It is a noradrenergic and specific serotonergic antidepressant that acts by antagonizing the  $\alpha_2$ -autoreceptors and  $\alpha_2$ -heteroreceptors and blocking postsynaptic 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors, leading to indirect enhancement of 5-HT<sub>1A</sub>-mediated neurotransmission. It enhances not only serotonergic neurotransmission but also noradrenergic neurotransmission, and it differs from venlafaxine and the SSRIs in that it is not a reuptake inhibitor.<sup>11</sup>

An overview of clinical trials investigating mirtazapine is given in Table 1.<sup>12</sup> In this overview, mirtazapine was shown to be significantly superior to placebo and trazo-

Figure 4. Change in HAM-D Factors at Endpoint With Mirtazapine or Placebo<sup>a</sup>



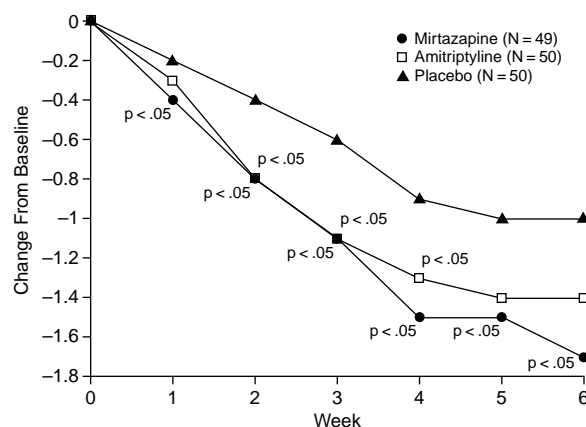
<sup>a</sup>Data from reference 13. Abbreviation: Bech = Bech Melancholia Scale.

done and comparable to amitriptyline and clomipramine in efficacy.

**Placebo-controlled studies.** In a meta-analysis of 5 short-term, placebo-controlled studies involving nearly 500 patients,<sup>13</sup> the efficacy of mirtazapine, as indicated by the 17-item HAM-D, was significantly superior to placebo at every timepoint (weeks 1 to 6). Furthermore, an analysis of the HAM-D factors at endpoint showed mirtazapine was significantly superior to placebo ( $p < .0001$ ) for melancholia, anxiety/somatization, sleep disturbance, and retardation (Figure 4).<sup>13</sup> A rapid response to mirtazapine treatment was observed, with significant differences being detected after only 1 week of treatment. Thus, in placebo-controlled studies, mirtazapine demonstrated a rapid onset of response and was found to be effective not only in depression but in depression with confounding anxiety and sleep disturbances.

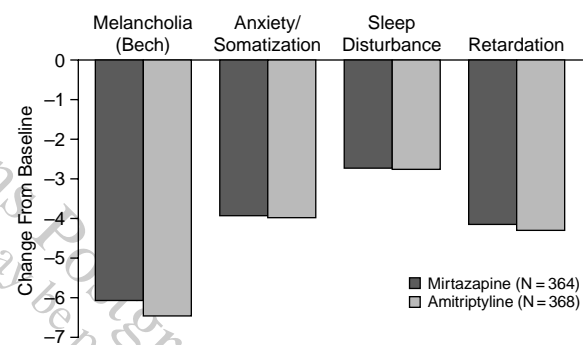
**Mirtazapine compared with TCAs.** Several trials have demonstrated that, unlike the SSRIs, mirtazapine has an efficacy that is at least equal to that of the TCAs. In a 6-week, double-blind study involving 163 patients with major depression, mirtazapine was found to be as effective as doxepin at reducing HAM-D and MADRS scores and had distinct advantages in terms of tolerability.<sup>14</sup> In a 6-week, double-blind, placebo-controlled comparison of mirtazapine with amitriptyline in patients with major depression, the changes in the HAM-D “depressed mood” item score showed significant ( $p < .05$ ) improvement compared with placebo for mirtazapine at weeks 1 to 6 and compared with amitriptyline at weeks 2 to 4 (Figure 5).<sup>15</sup> A meta-analysis of 5 double-blind studies comparing mirtazapine with amitriptyline demonstrated that the 2 agents had comparable efficacy.<sup>13</sup> Moreover, meta-analysis showed that the effect of mirtazapine on HAM-D factors at endpoint was similar to that of amitriptyline for melancholia, anxiety/somatization, sleep disturbance, and retardation (Figure 6).<sup>13</sup>

Figure 5. Changes in HAM-D Depressed Mood Item With Mirtazapine, Amitriptyline, or Placebo<sup>a</sup>



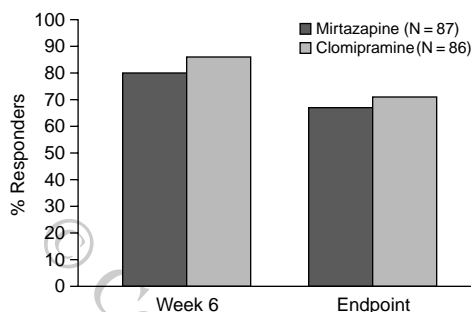
<sup>a</sup>Data from reference 15.

Figure 6. Change in HAM-D Factors at Endpoint With Mirtazapine or Amitriptyline<sup>a</sup>



<sup>a</sup>Data from reference 13.

**Difficult-to-treat patients.** Differences between dual-action and single-action antidepressants may be particularly marked in patients whose depression is difficult to treat, such as those with severe depression or who are hospitalized. Several studies have investigated the efficacy of mirtazapine in such patients. In a multicenter, double-blind, comparative study of mirtazapine and clomipramine involving 174 hospitalized depressed patients, the efficacy of mirtazapine was comparable to that of clomipramine as measured by the 17-item HAM-D.<sup>8</sup> Furthermore, there was also comparable efficacy for mirtazapine and clomipramine in the treatment of patients with particularly severe depression (HAM-D score  $\geq 25$ ). The response rate ( $\geq 50\%$  reduction in HAM-D score) was similarly high in the 2 treatment groups (Figure 7).<sup>8</sup> When compared with trazodone in a 6-week, double-blind study conducted in hospitalized depressed patients, mirtazapine was found to be significantly superior in terms of both efficacy and tol-

Figure 7. Responders (%) to Mirtazapine or Clomipramine Treatment<sup>a</sup>

<sup>a</sup>Data from reference 8. Responders had  $\geq 50\%$  decrease in total score on the 17-item HAM-D.

erability.<sup>16</sup> A double-blind study conducted in 251 hospitalized depressed patients compared the efficacy of mirtazapine with that of amitriptyline.<sup>17</sup> This study found that mirtazapine had efficacy comparable to that of amitriptyline and had a more favorable tolerability profile.

These results have been confirmed by several meta-analyses of available comparative data from difficult-to-treat patients.<sup>12,13,18</sup> In one meta-analysis of 814 depressed patients, the efficacy of mirtazapine, as indicated by the 17-item HAM-D, was comparable to that of the TCA amitriptyline in both outpatients and hospitalized patients.<sup>18</sup> The comparability of the effect of mirtazapine with that of amitriptyline has been confirmed in further analyses of patients with severe depression (defined as 17-item HAM-D score  $\geq 25$ ).<sup>12,13</sup> Mirtazapine therefore appears to be as effective as the TCAs for the treatment of severely depressed patients and hospitalized depressed patients.

**Treatment of elderly patients.** In addition, mirtazapine has been seen to be effective in the treatment of elderly depressed patients. The efficacy of mirtazapine in elderly patients as measured by the 21-item HAM-D and compared with amitriptyline, trazodone, and placebo is shown in Table 2.<sup>19,20</sup> A 6-week, double-blind study was conducted to compare mirtazapine and amitriptyline in 115 elderly depressed patients.<sup>20</sup> The efficacy of mirtazapine in these patients was comparable to that of amitriptyline at week 6 and endpoint. In a 6-week, placebo-controlled study conducted in 150 depressed outpatients aged over 55 years, mirtazapine exhibited superior efficacy to trazodone at both 6 weeks and endpoint, significantly so at week 6 ( $p < .05$ ).<sup>19</sup>

**Long-term treatment.** For optimal effectiveness, it is necessary to continue antidepressant therapy for at least 4 to 6 months after recovery from an acute episode of depression.<sup>21</sup> The long-term treatment of mirtazapine was compared to amitriptyline in a 2-year, double-blind, placebo-controlled, follow-up study including 217 de-

Table 2. Efficacy in Elderly Depressed Patients (21-Item HAM-D): Mirtazapine Versus Controls<sup>a</sup>

Drug	Baseline Score	Reduction in Score From Baseline	
		Week 6	Endpoint
Mirtazapine	26.8	-14.2	-12.0
Amitriptyline	25.9	-16.6	-14.3
Mirtazapine	24.6	-11.1*	-9.9
Trazodone	24.6	-7.6	-6.5
Placebo	23.5	-8.8	-7.9

<sup>a</sup>Data from references 19 and 20.

\* $p < .05$ .

pressed patients.<sup>22</sup> The efficacy of mirtazapine was comparable to that of amitriptyline at 20 weeks, but significantly superior to amitriptyline ( $p < .05$ ) at endpoint, and significantly superior to placebo ( $p < .05$ ) at both timepoints.

### Nefazodone

Nefazodone is an antidepressant that combines blockade of the 5-HT<sub>2</sub> receptor with serotonin uptake inhibition.<sup>23</sup> In short-term clinical trials, nefazodone produced clinical improvements greater than those with placebo and similar to those achieved with the TCA imipramine or the SSRIs paroxetine, sertraline, or fluoxetine.<sup>23</sup> In one study in hospitalized depressed patients, amitriptyline was superior to nefazodone, most probably due to less-than-optimal dosage.<sup>24</sup>

## CONCLUSIONS

Antidepressants that affect both the norepinephrine and serotonin systems are more effective than those with single neurotransmitter action. Mirtazapine is a novel antidepressant that has a dual action, acting on both noradrenergic and serotonergic neurotransmission. Unlike the SSRIs, mirtazapine has efficacy comparable to that of the TCAs in major depression. In addition, mirtazapine has shown good efficacy comparable to that of TCAs in difficult-to-treat depressed patients such as those with severe depression and in hospitalized patients and elderly patients. It is also safe and effective during long-term use.

**Drug names:** amitriptyline (Elavil and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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