Mirtazapine Versus Selective Serotonin Reuptake Inhibitors

Christopher Thompson, M.D., M.Phil., F.R.C.P., F.R.C.Psych.

The results of 3 completed comparative studies of mirtazapine versus selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine, and citalopram) are reviewed. The studies aimed to compare efficacy and tolerability in acute treatment of inpatients and outpatients with major depressive disorder. In comparative trials with fluoxetine, patients who had high baseline total 17-item Hamilton Rating Scale for Depression (HAM-D) and depressed mood item scores were included (scores ≥ 21 and ≥ 2, respectively). In the comparative trials with citalopram and paroxetine, the inclusion criteria were total Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 22 and 17-item HAM-D score ≥ 18. In all 3 studies, statistically significant and clinically relevant differences in favor of mirtazapine were evident on several outcome variables. Against citalopram and paroxetine, the differences in antidepressant efficacy were registered early in treatment but not later, thus suggesting potentially faster onset of efficacy of mirtazapine. These differences were demonstrated on both the 17-item HAM-D and MADRS scales. In addition, mirtazapine demonstrated an accelerated anxiolytic effect as shown by changes from baseline on the Hamilton Rating Scale for Anxiety. Tolerability of all studied compounds was very good, as reflected in a low percentage of premature terminations due to adverse events. On the other hand, differences in pharmacologic profiles between mirtazapine and SSRIs were reflected in their adverse events profiles. The results of these studies confirm that mirtazapine displays good efficacy—leading to an early relief of symptoms—in combination with good tolerability.

(J Clin Psychiatry 1999;60[suppl 17]:18–22)

Mirtazapine is a new noradrenergic and specific serotonergic antidepressant with a mode of action that differs from currently available antidepressants. Mirtazapine is an antagonist of α_2-autoreceptors and heteroreceptors, and its use is associated with an increased release of both norepinephrine and serotonin (5-HT).[1] This direct enhancement of noradrenergic-mediated and 5-HT_{1A}-receptor–mediated serotonergic neurotransmission is thought to be responsible for the antidepressant activity of mirtazapine.[2] Moreover, mirtazapine potently blocks 5-HT_2 and 5-HT_3 receptors, which may account for mirtazapine's anxiolytic and sleep-improving properties.[1]

Data from clinical trials have shown that mirtazapine has an overall efficacy similar to that of tricyclic antidepressants, but with a relative absence of cholinergic, adrenergic, and serotonergic side effects.[3,4] Moreover, it is relatively safe in an overdose situation.[3,4] Mirtazapine has been shown to be an effective antidepressant in both inpatients and outpatients and has also been seen to be beneficial for symptoms of anxiety and sleep disturbance associated with depression.[3]

This article will examine recent evidence on the comparison of mirtazapine with selective serotonin reuptake inhibitors (SSRIs). There have been 3 major trials of the new antidepressant mirtazapine versus the established SSRIs fluoxetine,[5] citalopram,[6] and paroxetine.[7] All 3 trials were multicenter, double-blind, randomized trials of both inpatients and outpatients with major depressive disorder. Study details and baseline characteristics for the trials are summarized in Table 1.

MIRTAZAPINE VERSUS FLUOXETINE

In a multicenter, double-blind, randomized trial, the efficacy and safety of mirtazapine was compared with that of fluoxetine.[5] Inpatients and outpatients with major depressive disorder and a 17-item Hamilton Depression Rating Scale (HAM-D) score ≥ 21 and HAM-D depressed mood (item 1) score ≥ 2 were selected from centers in Belgium, The Netherlands, and the United Kingdom. Patients were randomly assigned to receive mirtazapine, 15–60 mg/day, or fluoxetine, 20–40 mg/day, for 6 weeks. Mean daily dosage for the trial period was 39.8 mg in the mirtazapine group and 23.8 mg in the fluoxetine group.

The changes from baseline in 17-item HAM-D score for the mirtazapine and fluoxetine groups are shown in

From the Department of Psychiatry, Royal South Hampshire Hospital, Southampton, U.K.

Presented at the Scientific Expert Meeting, held in Monte Carlo, Monaco, February 26–27, 1999, and sponsored by NV Organon.

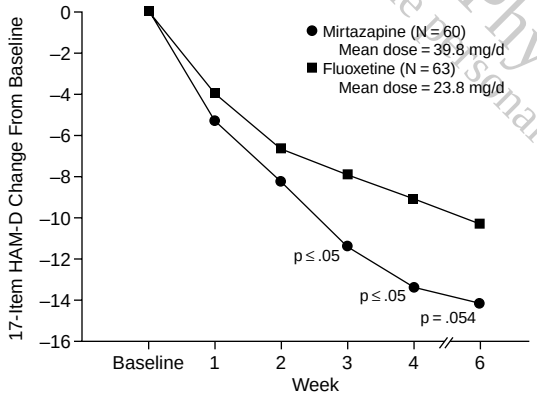
Reprint requests to: Christopher Thompson, Department of Psychiatry, Royal South Hampshire Hospital, Southampton SO14 0YG, United Kingdom.

Table 1. Mirtazapine Versus SSRIs: Study Details and Baseline Characteristics[a]

Variable	Comparator Drug		
	Citalopram	Fluoxetine	Paroxetine
Duration of trial, wk	8	6	6
Total number of patients[b]	269	123	250
Mirtazapine	136	60	127
SSRIs	133	63	123
Patient population	Inpatients, outpatients	Inpatients, outpatients	Inpatients, outpatients
Inclusion criteria	MADRS ≥ 22	HAM-D ≥ 21, depressed mood ≥ 2	HAM-D ≥ 18
Baseline scores (mean)			
Mirtazapine	MADRS 29.6	HAM-D 26.0	HAM-D 22.5
SSRIs	MADRS 29.1	HAM-D 26.1	HAM-D 22.5

[a]Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.
[b]Intent-to-treat population.

Figure 1. Mirtazapine Versus Fluoxetine: 17-Item HAM-D (change from baseline)[a]

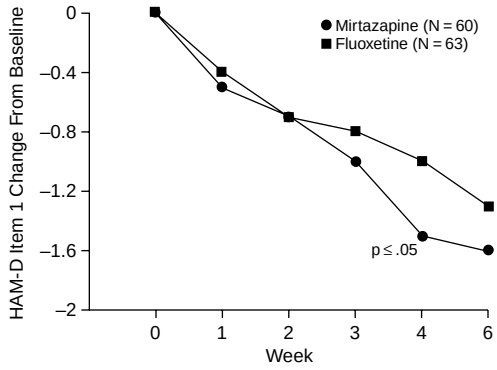


[a]Adapted from reference 5, with permission.

Figure 1. The decrease in HAM-D score was greater with mirtazapine than fluoxetine, and this difference was significant ($p \leq .05$) at weeks 3 and 4. Similarly, the decrease from baseline in the HAM-D item 1 score (depressed mood) was greater in the mirtazapine group than with fluoxetine, with a significant decrease at week 4 (Figure 2). Responder rates (≥ 50% reduction in HAM-D score) were higher for mirtazapine throughout the study, with a significant difference ($p < .05$) between the treatment groups at week 4 (Figure 3).

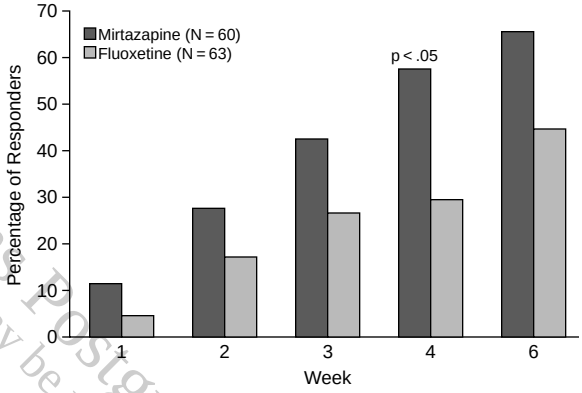
The percentage of patients who dropped out due to lack of efficacy was slightly less in the mirtazapine group (4.5%) compared with the fluoxetine group (7.5%), as was the percentage of patients who dropped out due to adverse events (mirtazapine, 10.6%; fluoxetine, 13.4%). Both treatment groups showed good tolerability. The adverse

Figure 2. Mirtazapine Versus Fluoxetine: Depressed Mood (HAM-D Item 1)[a]



[a]Data from reference 5.

Figure 3. Mirtazapine Versus Fluoxetine: Responders (≥ 50% reduction on HAM-D)[a]



[a]Adapted from reference 5, with permission.

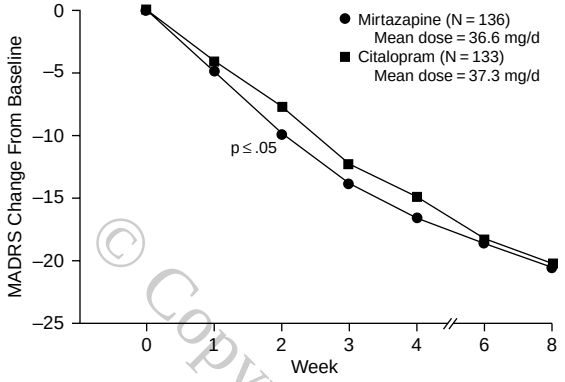
Table 2. Mirtazapine Versus Fluoxetine: Adverse Events Reported by > 5% of Patients in Either Treatment Group[a]

Adverse Event	Mirtazapine, % (N = 66)	Fluoxetine, % (N = 67)
Somnolence	18	13
Dry mouth	18	5
Headache	9	18
Nausea	3	10
Blurred vision	8	2
Dizziness	8	9
Drowsiness	11	8

[a]Adapted from reference 5, with permission.

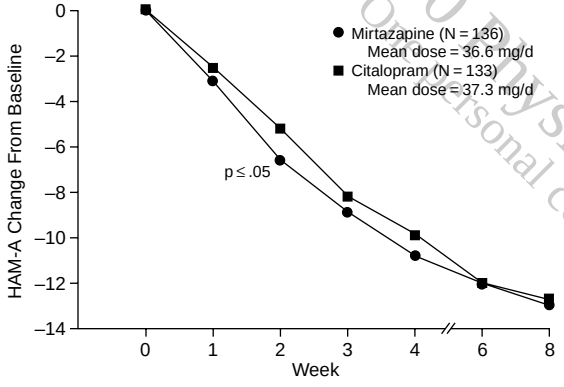
events reported in more than 5% of patients are given in Table 2. More patients taking fluoxetine complained of headache and nausea compared with those taking mirtazapine, while more patients taking mirtazapine complained of somnolence and dry mouth compared with those taking fluoxetine; there were no significant differences in adverse events between the treatment groups.

Figure 4. Mirtazapine Versus Citalopram: MADRS (change from baseline)[a]



[a]Data from reference 6.

Figure 5. Mirtazapine Versus Citalopram: HAM-A (change from baseline)[a]



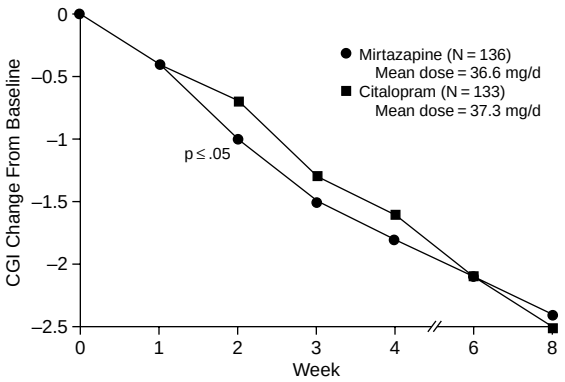
[a]Data from reference 6. Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

Overall, mirtazapine was found to have significantly superior efficacy to fluoxetine in the reduction in HAM-D score from baseline and the proportion of responders to treatment, and this effect was apparent during the first few weeks of treatment. The 2 treatments had comparable tolerability.

MIRTAZAPINE VERSUS CITALOPRAM

The antidepressant and anxiolytic efficacy and tolerability of mirtazapine were compared with those of citalopram in a multicenter, double-blind, randomized trial.[6] Inpatients and outpatients with major depressive disorder and a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥ 22 were selected from centers in Denmark, Finland, Norway, and Sweden. Patients were randomly assigned to mirtazapine, 15–60 mg/day, or citalopram, 20–60 mg/day, for 8 weeks. Mean daily dosage for the trial

Figure 6. Mirtazapine Versus Citalopram: CGI-Severity of Illness[a]



[a]Data from reference 6. Abbreviation: CGI = Clinical Global Impressions scale.

period was 36.6 mg in the mirtazapine group and 37.3 mg in the citalopram group.

The change from baseline in MADRS scores for mirtazapine and citalopram treatment groups is shown in Figure 4. The decrease in MADRS score was greater with mirtazapine than citalopram, and this difference was significant ($p \leq .05$) at week 2. Similarly, the decrease from baseline in Hamilton Rating Scale for Anxiety (HAM-A) and Clinical Global Impressions (CGI)-Severity of Illness scores was greater in the mirtazapine group than in the citalopram group, again with a significant decrease at week 2 (Figures 5 and 6). The CGI-Quality of Life score of patients taking mirtazapine was superior to that of patients taking citalopram at weeks 1 and 2, and significantly so at week 2 ($p \leq .05$), indicating an early onset of action for mirtazapine compared with citalopram. However, this advantage had disappeared by week 3. Responder rates (defined as much or very much improved on the CGI) were higher in the mirtazapine group for weeks 1 and 2, with no major difference between the treatment groups from week 3 onward.

The percentages of patients who dropped out due to lack of efficacy were similar for both treatment groups (mirtazapine, 2.8%; citalopram, 0.8%), as were the percentages of patients who dropped out due to adverse events (mirtazapine, 3.6%; citalopram, 3.0%). Both treatments were well tolerated. The adverse events reported in more than 5% of patients are given in Table 3. Significantly more patients taking citalopram complained of nausea and increased sweating compared with those taking mirtazapine, while significantly more patients taking mirtazapine complained of increased appetite and weight gain compared with those taking citalopram ($p < .05$).

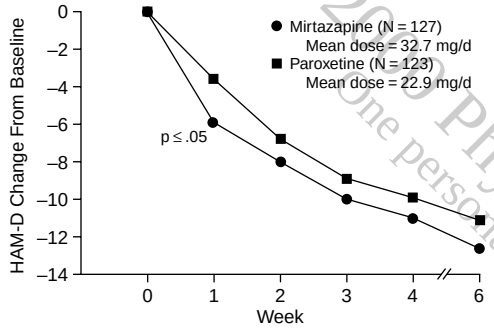
In conclusion, mirtazapine exhibited significantly superior efficacy to citalopram according to MADRS, CGI, and HAM-A scores at 2 weeks of treatment. Both drugs were well tolerated.

Table 3. Mirtazapine Versus Citalopram: Adverse Events Reported by > 5% of Patients[a]

Adverse Event	Mirtazapine, % (N = 136)	Citalopram, % (N = 133)
Nausea	10.2	20.2*
Weight increase	15.3*	4.5
Sweating increase	2.2	15.0*
Dry mouth	14.6	9.0
Headache	9.5	14.3
Fatigue	12.4	13.5
Appetite increase	8.8*	1.5
Dizziness	8.8	4.5
Excessive sedation	8.0	6.0
Diarrhea	2.9	6.0
Flu-like symptoms	5.1	2.3

[a]Data from reference 6.
*p < .05.

Figure 7. Mirtazapine Versus Paroxetine: HAM-D (change from baseline)[a]

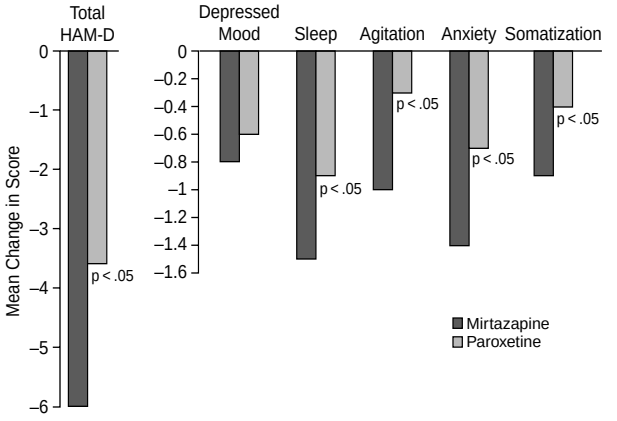


[a]Data from reference 7.

MIRTAZAPINE VERSUS PAROXETINE

In this multicenter, double-blind, randomized trial, the efficacy and tolerability of mirtazapine were compared with those of paroxetine.[7] Inpatients and outpatients with major depressive disorder and a 17-item HAM-D score ≥ 18 were selected from centers in Germany. Patients were randomly assigned to treatment with mirtazapine, 15–45 mg/day, or paroxetine, 20–40 mg/day, for 6 weeks. Mean daily dosage for the trial period was 32.7 mg in the mirtazapine group and 22.9 mg in the paroxetine group. In this study, the tolerability evaluation criteria were new or worsened symptoms in the UKU Side Effect Rating Scale and adverse events monitoring. The UKU scale was developed by Scandinavian psychiatrists and consists of a list of symptoms; the patient evaluates the presence and/or absence of each symptom and its severity at baseline and subsequent assessment points. Although frequently criticized for overestimating the incidence of adverse events, the UKU scale was used in this trial to evaluate the possible influences of treatment on sexual functioning, a purpose for which the scale has shown adequate sensitivity.[8]

Figure 8. Mirtazapine Versus Paroxetine: Week 1 Difference in Reduction From Baseline in HAM-D Total and Factor Scores[a]



[a]Data from reference 7.

Table 4. Mirtazapine Versus Paroxetine: Symptoms on the UKU Scale Occurring With a Frequency Difference of ≥ 5 Patients (4%) Between Treatment Groups[a]

Mirtazapine
Dry mouth
Weight gain
Paroxetine
Reduced duration of sleep
Tremor
Nausea/vomiting
Diarrhea
Orthostatic dizziness
Palpitations/tachycardia
Increased sweating
Diminished sexual desire
Orgasmic dysfunction
Headache

[a]Data from reference 7.

The changes from baseline in HAM-D score for the mirtazapine and paroxetine groups are shown in Figure 7. The decrease in HAM-D score was greater with mirtazapine than with paroxetine, and this difference was significant (p ≤ .05) at week 1. A breakdown at week 1 of the various HAM-D factors is shown in Figure 8. Mirtazapine was significantly (p < .05) superior to paroxetine for the sleep, agitation, anxiety, and somatization items, indicating the early onset of action of mirtazapine, particularly with regard to sleep and anxiety. Responder rates (≥ 50% reduction in HAM-D) were superior for mirtazapine at each study timepoint, but significantly so at weeks 1 and 4 (p ≤ .05).

Both treatments were well tolerated. All new or worsened symptoms in the UKU Side Effect Rating Scale that occurred with a frequency difference of ≥ 5 patients (4%) between treatment groups are shown in Table 4.

The UKU symptoms more frequently reported with mirtazapine and paroxetine are shown in Table 5. The rel-

Table 5. Mirtazapine Versus Paroxetine: Symptoms on the UKU Scale Occurring More Frequently in Each Treatment Group[a]

UKU Symptoms	Mirtazapine, % (N = 127)	Paroxetine, % (N = 126)
Nausea and vomiting	7.9***	26.2
Orgasmic dysfunction	3.1**	13.5
Tremor	7.9*	17.5
Weight gain	40.2	24.6**
Headache	18.9	30.2
Weight loss	17.3	27.8
Increased sweating	15.0	24.6
Diarrhea	9.5	17.5

[a]Data from reference 7.
*p < .05. **p < .01. ***p < .001.

ative frequency of these symptoms was significantly different between the 2 treatment groups (Fisher exact test) in favor of mirtazapine for nausea/vomiting, orgasmic dysfunction, and tremor ($p < .05$) and in favor of paroxetine for weight gain ($p < .01$).

CONCLUSION

In each of these comparative trials of mirtazapine with established SSRIs (fluoxetine, citalopram, and paroxetine), mirtazapine showed greater or more rapid reductions in HAM-D or MADRS score than did the SSRI, suggesting an earlier onset of efficacy for mirtazapine. All treatments showed good tolerability, with only a few significant differences in frequency of adverse events, which reflects the different pharmacologic profiles of the treatment drugs.

Drug names: citalopram (Celexa), fluoxetine (Prozac), mirtazapine (Remeron), paroxetine (Paxil).

REFERENCES

1. de Boer T. The pharmacologic profile of mirtazapine. J Clin Psychiatry 1996;57(suppl 4):19–25
2. de Boer T. The effects of mirtazapine on central noradrenergic and serotonergic neurotransmission. Int Clin Psychopharmacol 1995;10(suppl 4): 19–23
3. Kasper S, Praschak-Rieder N, Tauscher J, et al. A risk-benefit assessment of mirtazapine in the treatment of depression. Drug Saf 1997;17:251–264
4. Montgomery SA. Safety of mirtazapine: a review. Int Clin Psychopharmacol 1995;10:39–47
5. Wheatley DP, van Moffaert M, Timmerman L, et al. Mirtazapine efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe depressive disorder. J Clin Psychiatry 1998;59:306–312
6. Agren H, Leinonen E, Skarstein J, et al. Efficacy and tolerability of mirtazapine vs citalopram: a double-blind, randomized study in patients with major depressive disorder [abstract]. In: Scientific Abstracts of the 37th Annual Meeting of the American College of Neuropsychopharmacology; Dec. 14–18, 1998; Las Croabas, Puerto Rico: 320
7. Benkert O, Szegedi A, Kohnen R. Rapid onset of therapeutic action in major depression: a comparative trial of mirtazapine and paroxetine [abstract]. In: Scientific Abstracts of the 37th Annual Meeting of the American College of Neuropsychopharmacology; Dec. 14–18, 1998; Las Croabas, Puerto Rico: 311
8. Phillip M, Kohnen R, Benkert O. A comparison study of moclobemide and doxepin in major depression with special reference to effects on sexual dysfunction. Int Clin Psychopharmacol 1993;7:149–153