Tolerability and Patient Compliance

Steven P. Roose, M.D.

Currently available antidepressants interact with several types of receptors, which may explain both wanted and unwanted effects of these drugs. These effects are different and distinctive, and knowledge about them may help clinicians understand differences between compounds in terms of their tolerability profiles. Given roughly comparable efficacy, tolerability profile is the critical determinant in selecting an antidepressant medication for a particular patient. In addition, tolerability is inseparably linked to patient compliance, both in acute and long-term treatment, and ultimately to overall success of treatment. Refinement in pharmacologic profiles of all newly introduced antidepressants resulted in overall advantages in tolerability in comparison with older tricyclic compounds. However, differences in receptor interactions between antidepressants are directly reflected in tolerability (adverse event) profiles. Among new antidepressants, mirtazapine and the selective serotonin reuptake inhibitors share favorable overall tolerability and safety, especially with respect to low premature termination rates because of adverse events, cardiac safety, and safety in overdose. However, the different pharmacologic profile of mirtazapine is reflected in its different tolerability profile. Because of interactions with the histamine (H_1) receptor, mirtazapine may be related to transient initial somnolence and weight gain in some patients. Its serotonin-2 ($5\text{-}HT_2$)–blocking properties may account for lack of sexual dysfunction, insomnia, nervousness, and agitation. Mirtazapine's $5\text{-}HT_3$-blocking properties are unique among all currently available antidepressants and may account for lack of gastrointestinal adverse events.

(J Clin Psychiatry 1999;60[suppl 17]:14–17)

Currently, there is a vast range of antidepressants available from which to choose when treating a patient who has depression. These antidepressants are of several types or classes of agent, each with a different pharmacology and mode of action. It is because of their differential modes of action and influence on different types of neurotransmitters and receptors that antidepressants have differing side effect profiles. Given that many antidepressants have comparable levels of efficacy, the tolerability profile is often a critical determinant when selecting an antidepressant agent for a particular patient. Furthermore, a favorable tolerability profile is essential to ensure good patient compliance with the treatment regimen, thereby enabling the agent to exert its optimum efficacy. This article reviews the tolerability and compliance associated with the latest antidepressants.

From the Department of Psychiatry, Late Life Depression Research Clinic, New York State Psychiatric Institute, Columbia University, New York.

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

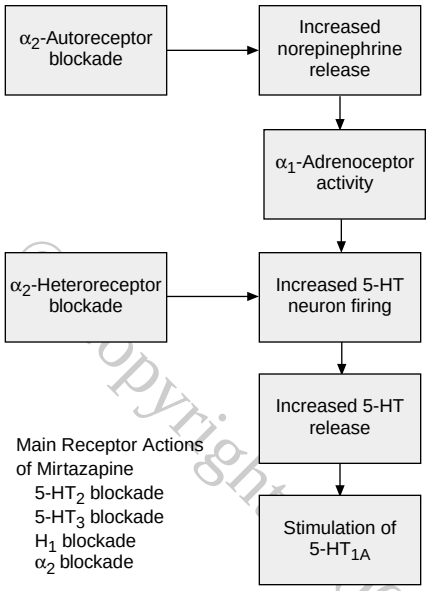
Reprint requests to: Steven P. Roose, M.D., Department of Psychiatry, Late Life Depression Research Clinic, New York State Psychiatric Institute, 1051 Riverside Dr., Unit 98, New York, NY 10032.

EFFECTS OF DIFFERING MODES OF ACTION

Each antidepressant class has a different pharmacology and mode of action, resulting in distinct tolerability profiles. As their name suggests, selective serotonin reuptake inhibitors (SSRIs) inhibit the reuptake of serotonin (5-HT), thereby causing synaptic concentrations of 5-HT to rise. Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), acts by inhibiting the reuptake of serotonin and norepinephrine, thereby increasing synaptic concentrations of 5-HT and norepinephrine.[1] Another new antidepressant, mirtazapine, is a noradrenergic and specific serotonergic antidepressant (NaSSA). It enhances both noradrenergic and serotonergic neurotransmission and specifically blocks $5\text{-}HT_2$, $5\text{-}HT_3$, and histamine type 1 (H_1) receptors. Autosynaptic and heterosynaptic α_2 receptor blockade leads to the release of norepinephrine and 5-HT and the stimulation of $5\text{-}HT_{1A}$, as shown in Figure 1.[2]

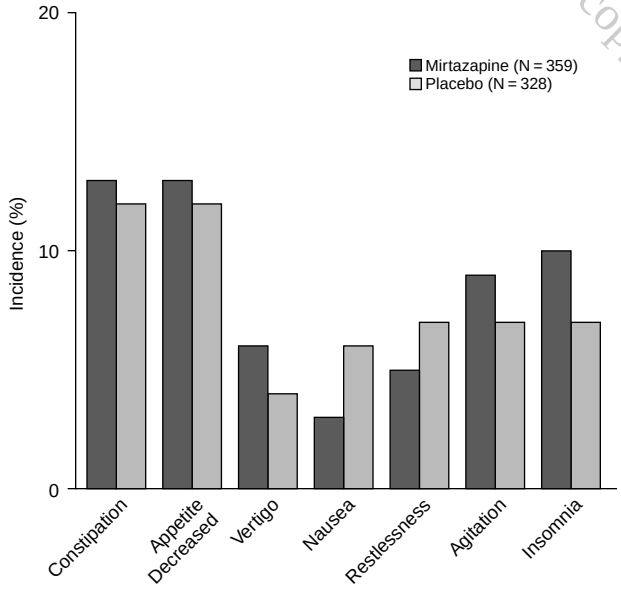
Antidepressants affect a number of serotonin targets, and stimulation of each target gives rise to a variety of side effects. For example, stimulation of $5\text{-}HT_{2A}$ receptors causes behavioral activation, insomnia, anxiety, and sexual dysfunction, whereas stimulation of $5\text{-}HT_{2C}$ receptors causes irritability and decreased appetite. Stimulation of $5\text{-}HT_3$ causes nausea and vomiting. Other postsynaptic targets include H_1 blockage, which can lead to sedation and weight gain, and α_1 blockade, which is linked with

Figure 1. Mode of Action of Mirtazapine[a]



[a]Data from reference 2.

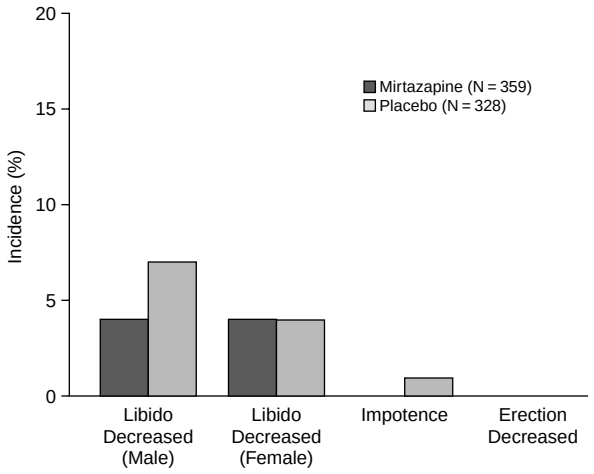
Figure 2. Incidence of Serotonergic Adverse Events in Patients Taking Mirtazapine or Placebo[a]



[a]Data from reference 4.

postural hypotension, dizziness, and reflex tachycardia. Thus, mirtazapine might be expected to be associated with sedative effects and weight gain and to be free of gastrointestinal effects. From their pharmacologic profile, SSRIs would be associated with gastrointestinal effects, sexual dysfunction, and anxiety.

Figure 3. Incidence of Sexual Dysfunction in Patients Taking Mirtazapine or Placebo[a]



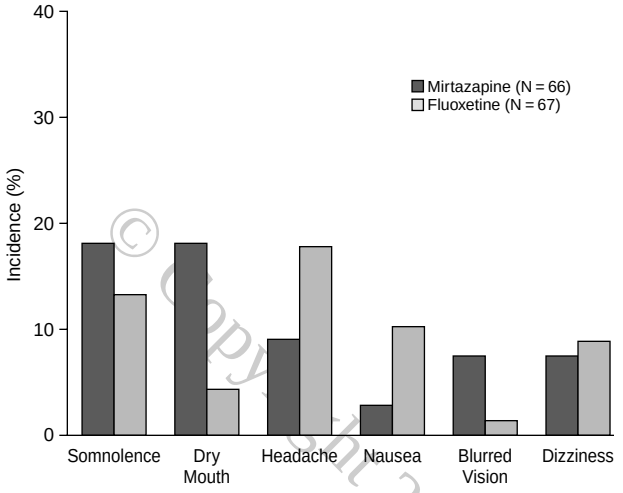
[a]Adapted from reference 4, with permission.

TOLERABILITY

The NaSSA mirtazapine has been shown to have a favorable side effect profile.[3] In an overview of the safety data accumulated on this agent, significantly fewer patients reported adverse experiences while taking mirtazapine (65%) than while taking placebo (76%).[4] The only side effects that occurred in significantly more mirtazapine recipients than placebo recipients were dry mouth, drowsiness, sedation, increased appetite, and weight increase. Headache and weight increase were reported by significantly more placebo patients than mirtazapine recipients. The comparative incidence of serotonergic adverse events with patients taking mirtazapine and those taking placebo is shown in Figure 2 and was generally similar. Sexual dysfunction is a common side effect of antidepressant treatment, but was markedly lower in those taking mirtazapine than in placebo recipients (Figure 3).

Because of its novel mode of action, mirtazapine lacks many of the side effects associated with SSRI use, such as gastrointestinal effects, sexual dysfunction, headache, restlessness, anxiety, and insomnia.[5] The tolerability of mirtazapine was compared with that of the SSRI fluoxetine in a double-blind, randomized study conducted in 133 patients with major depression.[6] The results of this study are presented in Figure 4. While mirtazapine use was associated with more reports of dry mouth, blurred vision, and somnolence than was fluoxetine use, the incidences of headache, nausea, and dizziness were lower with mirtazapine. A similar study was conducted in 270 depressed patients and compared the effects of mirtazapine with the effects of the SSRI citalopram.[7] Mirtazapine was associated

Figure 4. Incidence of Adverse Events in Patients Taking Mirtazapine or Fluoxetine[a]

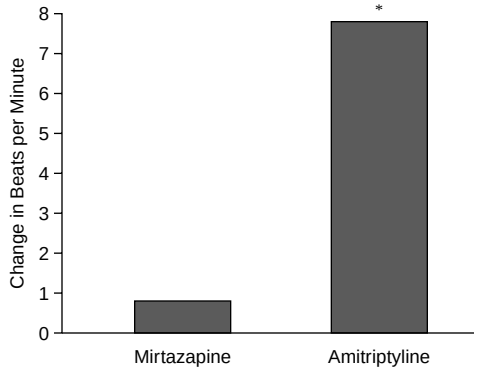


[a]Data from reference 6.

with a significantly higher incidence of appetite and weight increase but significantly lower incidences of nausea and sweating. The tolerability of mirtazapine has been compared with that of an additional SSRI, paroxetine, in another recent study.[8] This study also demonstrated that mirtazapine had significantly lower incidences of nausea, vomiting, sweating, and tremor, but was associated with significantly more reports of weight increase and flu-like symptoms.

The tolerability of mirtazapine has been established in a long-term study.[9] In a double-blind, placebo-controlled study conducted in 217 patients, the tolerability of mirtazapine was compared with that of amitriptyline over a 2-year period.[9] Mirtazapine was associated with significantly less dry mouth, drowsiness, constipation, and tremor than the tricyclic antidepressant (TCA), but was associated with significantly more weight gain. Mirtazapine's tolerability has also been investigated in elderly patients. When safety data in patients over 65 years taking mirtazapine were compared with those in patients 65 years or younger, a similar tolerability profile was found in each age group.[4] The differences that were detected—increased constipation, dizziness, and dry mouth in the elderly recipients—were attributed to age-related effects rather than the drug itself. Postmarketing surveillance[5] of over 1,500,000 patients treated with mirtazapine demonstrated that the drug was free of gastrointestinal effects, had no significant effects on vital signs or liver enzymes, and did not induce neutropenia. It was also found to be safe in cases of overdose. Moreover, a recent study[10] in which 10,405 depressed outpatients received mirtazapine suggests that somnolence and weight gain occurred only rarely in everyday clinical practice.

Figure 5. Changes From Baseline in Heart Rhythm in Patients Taking Mirtazapine or Amitriptyline[a]



[a]Data from reference 4.
*p < .001 vs. mirtazapine.

Cardiac Safety

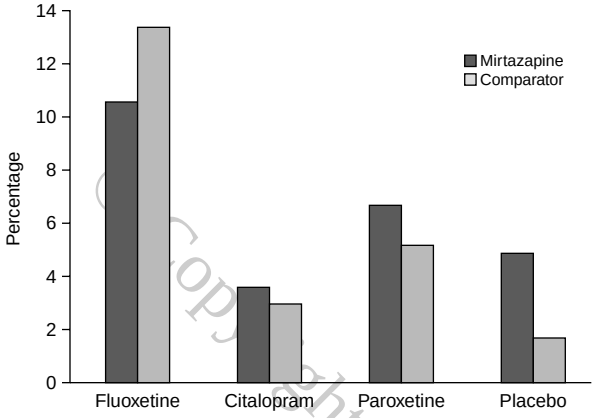
The cardiovascular effects of an antidepressant are an important component of its overall tolerability. Coronary artery disease is a common problem (its prevalence is 18% to 26%),[11] and there is a high incidence of depression after myocardial infarction. One week after myocardial infarction, 16% of patients suffer from major depression. The presence of depression is associated with increased mortality and, in post–myocardial infarction depression, is a significant indicator of cardiac mortality. It is therefore important to consider the cardiovascular safety of a given antidepressant, particularly when prescribing for patients with comorbid cardiac illnesses, especially the elderly.[12]

The TCA nortriptyline has been shown to be associated with significant increases in heart rate, and the SSRI paroxetine is associated with significant increases in systolic blood pressure.[12] Mirtazapine does not have detrimental effects on heart rate or blood pressure. Any changes in vital signs observed with mirtazapine were similar to those found in placebo recipients.[4] In a comparative evaluation of the safety of mirtazapine and amitriptyline, significantly greater increases in heart rate were recorded with amitriptyline than with mirtazapine (Figure 5).[4] When compared with the SSRIs citalopram, paroxetine, and fluoxetine, mirtazapine was not associated with any significant changes in blood pressure.[6–8]

COMPLIANCE

Poor patient compliance with drug treatment can often be problematic in patients with depression, particularly when long-term treatment is instituted. However, it is important that treatment for depression is continued for many months to ensure that the condition of the patient, once recovered, is maintained. Thus, good patient compliance is required to ensure maximum efficacy of a particular anti-

Figure 6. Incidence of Drug-Related Dropouts Due to Adverse Events in Patients Taking Mirtazapine Compared With Selective Serotonin Reuptake Inhibitors and Placebo[a]



[a]Data from reference 13.

depressant treatment. Patient compliance depends on several factors: the patient's awareness of the need for treatment; the efficacy of the agent, particularly regarding an early onset of action; and the ease and convenience of the drug regimen. However, a major factor in determining patient compliance is the tolerability profile of the particular antidepressant prescribed. The number of patients dropping out of a clinical trial due to adverse events is a good indication of the effects of drug tolerability on patient compliance.

The results of clinical trials suggest that depressed patients are more likely to comply with treatment with the NaSSA mirtazapine than with conventional TCA therapy. In an overview of available safety data on mirtazapine, the drug was shown to be associated with significantly fewer dropouts due to adverse events than the TCA amitriptyline.[4]

The results of a recent study[13] have demonstrated that the risk of patients dropping out of a study due to adverse effects was significantly greater for TCAs than for the majority of SSRIs investigated. This effect in favor of SSRIs was most marked when the data for all SSRIs were combined ($p < .0001$). When the proportion of drug-related dropouts due to adverse events in patients treated with the NaSSA mirtazapine was compared with that of SSRI recipients, mirtazapine was associated with a similar number of dropouts due to adverse events as citalopram and paroxetine and slightly fewer than with fluoxetine (Figure 6).

CONCLUSIONS

The tolerability profile of an antidepressant is an important factor governing the choice of treatment and has considerable influence on patient compliance, particularly during long-term use. The different mode of action of the NaSSA mirtazapine from that of TCA or SSRI antidepressants means that it has a different side effect profile from other antidepressant agents and, in particular, lacks serotonergic side effects. Mirtazapine has an overall tolerability and safety profile that is comparable to that of SSRIs, but unlike SSRIs, it is not associated with gastrointestinal symptoms, sexual dysfunction, or increased heart rate.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), fluoxetine (Prozac), mirtazapine (Remeron), nortriptyline (Pamelor and others), paroxetine (Paxil), venlafaxine (Effexor).

REFERENCES

1. Debonnel G, Blier P, Saint-Andre E, et al. Differential effects of a low and of a high dose of venlafaxine on serotonin and norepinephrine reuptake processes in major depression [abstract]. In: Scientific Abstracts of the 36th Annual Meeting of American College of Neuropsychopharmacology; Dec 8–12, 1997; Waikoloa, Hawaii:238
2. De Boer T. The pharmacologic profile of mirtazapine. J Clin Psychiatry 1996;57(suppl 4):19–25
3. Kasper S, Praschak-Reider 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(suppl 4):37–45
5. Davis JM, Giakas WJ. Mirtazapine: the first million patients [abstract]. In: Scientific Abstracts of the 37th Annual Meeting of the American College of Neuropsychopharmacology; Dec 14–18, 1998; Las Croabas, Puerto Rico: 304
6. Wheatley DP, van Moffaert M, Timmerman L, et al. Mirtazapine efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. J Clin Psychiatry 1998;59:306–312
7. 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
8. 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
9. Montgomery SA, Reimitz P-E, Zivkov M. Mirtazapine versus amitriptyline in the long-term treatment of depression: a double-blind placebo-controlled study. Int Clin Psychopharmacol 1998;13:63–73
10. Zivkov MV, Kreutzenbeck H-J. The use of mirtazapine in primary care [abstract]. In: New Research Program and Abstracts of the 151st Annual Meeting of the American Psychiatric Association; June 4, 1998; Toronto, Ontario, Canada. Abstract NR668:249
11. Goldberg RJ. Depression in medical patients. R I Med 1993;76:391–396
12. Roose SP, Laghrissi-Thode F, Kennedy JS, et al. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. JAMA 1998;279:287–291
13. Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. Depress Anxiety 1998;7 (suppl 1):11–18