The Role of Mirtazapine in the Pharmacotherapy of Depression

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *summarizes the presentations and panel discussion from a 2-day Scientific Expert Meeting held in Athens, Greece, March 24–25, 2000. This meeting was sponsored by an unrestricted educational grant from NV Organon, Oss, the Netherlands.*

The meeting, "Building Confidence from Patients' Satisfaction," was chaired by Martin B. Keller, M.D., Professor and Chairman of the Department of Psychiatry and Human Behavior, Brown University School of Medicine, Providence, R.I., and cochaired by Roger M. Pinder, Ph.D., D.Sc., International Medical Director CNS and Cardiovascular, Organon Inc., West Orange, N.J.

Participants in the expert meeting and panel discussion are listed at the end of this section.

Pharmacologic Mechanisms of Antidepressant Action

Over more than 30 years, evidence has accumulated confirming the hypothesis that norepinephrine and serotonin play pivotal roles in the mechanism of action of antidepressant drugs, stated Dr. Alan F. Schatzberg. Many antidepressants from distinct pharmacologic classes are currently available, but all affect one or both of these neurotransmitter systems. The first antidepressants—the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)—act mainly on noradrenergic and serotonergic systems, but their affinity for other neuronal systems, such as cholinergic, α_1-adrenergic, dopaminergic, and histaminergic, and quinidine-like effects contribute to their poor tolerability profiles. In contrast, the selective serotonin reuptake inhibitors (SSRIs: e.g., fluoxetine, citalopram, paroxetine, sertraline) have no effect on norepinephrine, and affinity for other receptors differs between the individual agents. In contrast, the norepinephrine reuptake inhibitor (NRI) reboxetine has no effect on serotonin uptake. The serotonergic-norepinephrine reuptake inhibitors (SNRIs: e.g., venlafaxine) tend to act on both neurotransmitters only at high dosages, and they have minimal affinity for other neuronal systems. Another antidepressant with a distinct mode of action is the noradrenergic and specific serotonergic antidepressant (NaSSA) mirtazapine.

For most antidepressants that rely only on reuptake of serotonin for their efficacy (SSRIs), there is a delay in onset of action of about 3 to 4 weeks.[1] It is thought that the increase in serotonin release at initiation of treatment causes inhibition of serotonin-1A (5-HT_{1A}) receptors, thereby decreasing serotonergic cell firing and reducing serotonin release. Only after several weeks of treatment does normalization of serotonergic cell firing occur.[1]

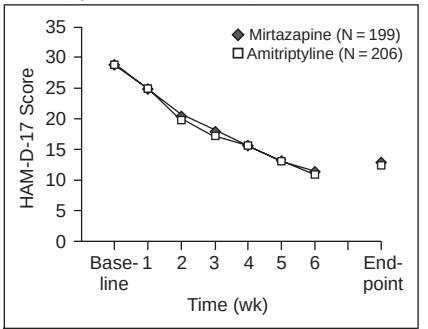
By contrast, noted Dr. Schatzberg, the mode of action of the world's first NaSSA, mirtazapine, results in a rapid onset of efficacy. It is the only antidepressant to specifically increase serotonergic firing rate. Mirtazapine acts by blocking α_2-adrenoceptors on noradrenergic neurons, enhancing norepinephrine release.[1] The increased levels of norepinephrine act on α_1-adrenoceptors on the serotonergic cell body to increase serotonergic cell firing, resulting in enhanced serotonin release at the nerve terminal. In this way, mirtazapine induces an immediate and persistent increase in serotonergic cell firing. Blockade of the α_2-heteroreceptors on the 5-HT nerve terminals further enhances serotonin release by preventing the inhibitory effect of norepinephrine. Moreover, mirtazapine blocks the 5-HT_2 and 5-HT_3 receptors, preventing many of the undesirable side effects seen with SSRIs and SNRIs (e.g., insomnia, sexual dysfunction, nausea), and, therefore, it selectively stimulates 5-HT_1 receptors, which are associated with antidepressant and anxiolytic effects. Hence, on the basis of pharmacologic mechanisms, mirtazapine has the potential for efficacy against depression and anxiety, with a more rapid onset of action than TCAs and SSRIs, and a low potential for TCA- and SSRI-associated side effects. ❑

Clinical Efficacy of Mirtazapine

Although the TCAs and MAOIs are still in use today, they have largely been replaced in first-line therapy by better tolerated drugs, such as the SSRIs, said Professor Chris Thompson. Overall, the efficacy of TCAs and SSRIs appears to be equivalent, but there is some evidence to indicate that TCAs may be more effective in severely depressed and hospitalized patients.[2,3] This is perhaps due to reuptake inhibition of both serotonin and norepinephrine. However, the new dual-action drugs, such as venlafaxine and mirtazapine, appear to have similar efficacy to the TCAs in all patients, including the severely depressed.

The NaSSA mirtazapine has consistently demonstrated equivalent efficacy to the TCAs in moderate-to-severe depression[4–6] (Figure 1). Comparisons with SSRIs in 3 randomized, double-blind trials looking at inpatients and outpatients have also yielded favorable results for mirtazapine, stated Professor Thompson. One 6-week study versus fluoxetine revealed that mirtazapine caused a larger decrease in Hamilton Rating Scale for Depression (HAM-D) scores throughout the study, reaching significance at weeks 3 and 4 ($p \leq .05$), and at week 6, a clinically significant 4-point difference was seen ($p = .054$).[7] In addition, more mirtazapine-treated subjects were classified as HAM-D responders, a significant difference at week 4 ($p < .05$).[7] In a comparative 8-week study of mirtazapine and citalopram, mirtazapine showed superior efficacy in the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Anxiety (HAM-A), and Clinical Global Impressions (CGI) Severity of Illness and Quality of Life scores at day 14 ($p \leq 05$).[8] When comparing mirtazapine with paroxetine in a 6-week trial, the efficacy measures (HAM-D-17: total score, responders [defined as ≥ 50% reduction in HAM-D-17], and individual items in the factor analysis) improved more substantially with mirtazapine during the first 4 weeks.[9] Statistically significant differences were seen for total score and individual factors (sleep, agitation, anxiety, somatization) at week 1, and there were more mirtazapine responders at weeks 1 and 4 ($p \leq .05$). These results suggest a faster onset of action against general measures of depression and anxiety for mirtazapine compared with the SSRIs. ❑

Figure 1. Efficacy of Mirtazapine vs. Amitriptyline in Severe Depression[a]



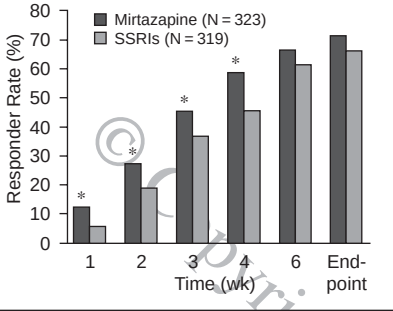
[a]Data from Kasper et al.[5] Severe depression defined as baseline 17-item Hamilton Rating Scale for Depression (HAM-D-17) score of ≥ 25.

The Early Onset of Action of NaSSAs

Assessing the onset of action of antidepressants is rarely the primary objective of trials and tends to be analyzed by post hoc analyses of existing data from efficacy studies, stated Dr. Michael E. Thase. The most straightforward method developed to determine onset of action simply identifies the earliest timepoint at which there is a statistically significant difference in responders (≥ 50% reduction in HAM-D-17 total score from baseline) between 2 treatment groups.[10,11] Huitfeldt and Montgomery[11] adapted this definition so that time to onset is the point when a statistically significant difference translates into a clinical advantage in absolute change from baseline on the HAM-D-17 or MADRS between treatment groups. The use of pattern analysis, derived from weekly assessments of the CGI-Change score, can identify whether an early response is sustained or diminishes, but strict exclusion criteria can limit its application.[12,13] The method of survival analysis is sufficiently sensitive to detect small changes in time to onset of improvement, and modifications to the original approach have allowed analysis of first sustained response.[14,15]

The delay to onset of action of 3 to 4 weeks is a limitation of most antidepressants, said Dr. Thase. Growing evidence suggests that mirtazapine, the world's first antidepressant classed as a NaSSA, has a more rapid onset of action than SSRIs. Pooled data from 3 double-blind comparisons of mirtazapine with the SSRIs fluoxetine, paroxetine, and citalopram support this conclusion (data on file, NV Organon). The earlier response with mirtazapine was seen consistently in various methods of analysis. More patients were rated as "much" or "very much improved" on the CGI-Change score, which reached significance at week 1 ($p \leq .05$), and there were more responders with ≥ 50% reduction in the HAM-D-17 or MADRS at weeks 1 to 4 ($p \leq .05$) and more Bech Melancholia Factor responders at weeks 1, 3, 4, and 6 ($p \leq .05$) (Figure 2).[16] Mirtazapine demonstrated an earlier onset of action than the SSRIs by yielding statistically significantly higher absolute change from baseline in HAM-D-17 total score from week 1 onward ($p \leq .05$) and in the Bech Melancholia Factor at week 1 ($p \leq .05$). Furthermore, remission rates (HAM-D-17 total score of ≤ 7 or MADRS total score of ≤ 12) were significantly higher with

Figure 2. Responder Rates of Mirtazapine vs. SSRIs (Fluoxetine, Paroxetine, Citalopram)[a]



[a]Data from Pinder.[16] Response defined as ≥ 50% reduction in HAM-D-17 or MADRS score.
*p ≤ .05 vs. fluoxetine/paroxetine/citalopram.

mirtazapine than the SSRIs at weeks 3 and 4 (p ≤ .05), Dr. Thase noted.

Pattern analysis of the pooled data showed that significantly more mirtazapine-treated patients experienced an early persistent response on the HAM-D-17 or MADRS (p < .05). Survival analysis also revealed a statistically significant earlier response with mirtazapine compared with fluoxetine and paroxetine (p = .008). Time to first remission was shorter with mirtazapine (p = .03), and, at week 3, only 15% of the patients taking SSRIs were in remission compared with 28% taking mirtazapine.

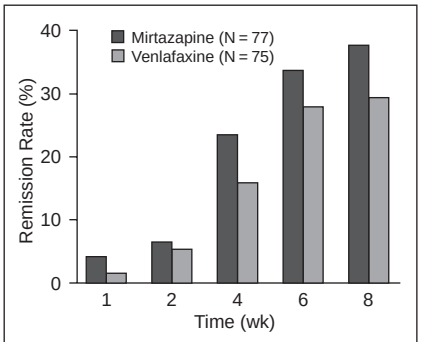
These data, perhaps resulting from mirtazapine's unique mechanism of action (i.e., an immediate increase in serotonergic firing rate), provide evidence for the early onset of efficacy of mirtazapine. Planned prospective studies specifically designed to assess the onset of action of mirtazapine compared with SSRIs may further substantiate these findings. Dr. Thase highlighted that the several weeks' delay in onset of action seen with SSRIs and SNRIs can impact patients' confidence in both their medication and their doctor. Hence, a fast-acting antidepressant may help doctors build a good therapeutic alliance with their patients and also make it easier for patients to accept and comply with their treatment. ❑

Comparing the New Generation of Dual-Action Antidepressants

It has been proposed that antidepressant drugs with actions on both serotonergic and noradrenergic neurotransmission may be more effective than drugs with modulation of either system alone, stated Professor Julien-Daniel Guelfi. This may explain the data showing superior efficacy and higher remission rates with the SNRI venlafaxine compared with the SSRIs fluoxetine and paroxetine in severe depression.[17–19]

Professor Guelfi presented results from an 8-week, double-blind, randomized study which indicate that mirtazapine may have additional benefits over venlafaxine in severely depressed patients.[20] Due to the severity of illness, the doses for each drug were rapidly titrated up—the dosage schedule allowed adjustments within the range of 15–60 mg/day for mirtazapine and 75–375 mg/day for venlafaxine. The overall mean doses were 49.5 mg/day of mirtazapine and 255 mg/day of venlafaxine. Both drugs demonstrated similar results with a trend toward better improvement and more responders and more remitters (measured by MADRS and HAM-D-17) with mirtazapine (Figure 3). Similar findings for venlafaxine and mirtazapine were seen in the HAM-D factor analysis for

Figure 3. Mirtazapine vs. Venlafaxine: Remitters on the HAM-D-17[a]



[a]Data from Guelfi et al.[20] Remission defined as HAM-D-17 score ≤ 7.

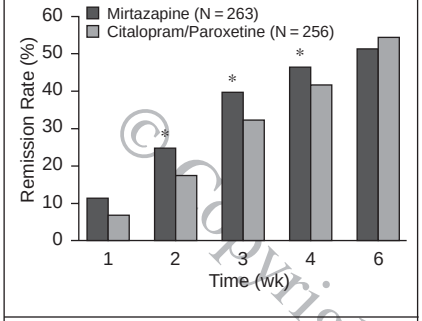
anxiety/somatization, weight loss, and retardation, although there was a significant difference in the sleep disturbance factor favoring mirtazapine (p = .001). In this study, more than a 10% difference in adverse events between the drugs was reported for nausea, constipation, weight loss, and increased sweating with venlafaxine and weight gain with mirtazapine. However, the number of discontinuations was significantly different in this study—5.1% of mirtazapine-treated patients prematurely discontinued due to side effects compared with 15.2% of venlafaxine-treated patients (p < .05). Therefore, mirtazapine seems to be at least equal in efficacy to venlafaxine and better tolerated in this population of severely depressed patients, concluded Professor Guelfi. ❑

Depression-Related Anxiety, Sleep Disturbances, and Sexual Dysfunction

Anxiety symptoms are reportedly experienced by 53.7% of patients with major depression.[21] Such symptoms can impact the severity of depressive illness, resulting in more psychosocial impairment, poorer response to treatment, and greater risk of suicide.[22,23]

Some existing antidepressants, such as the SSRIs, can actually cause or worsen anxiety symptoms early in treatment, stated Dr. Robert M. A. Hirschfeld, but newer therapies, such as mirtazapine, appear to be beneficial. In a meta-analysis of patients with a baseline HAM-D anxiety/agitation

Figure 4. Remission Rates in Anxiety Symptoms for Mirtazapine vs. SSRIs[a]



[a]Data from van Hensbeek et al.[26] Remission defined as HAM-A total score ≤ 8.
*p ≤ .05 vs. citalopram/paroxetine.

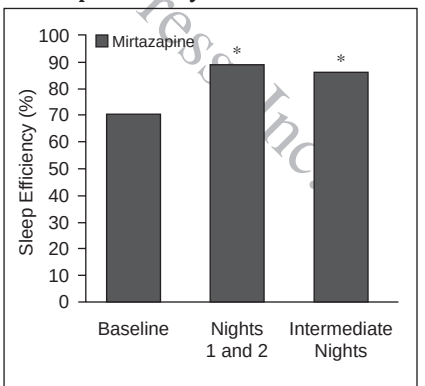
score of ≥ 6, treatment with mirtazapine reduced anxiety/agitation symptoms significantly when compared with placebo ($p \leq .05$).[24] Differences between SSRIs and mirtazapine in reducing anxiety have also been reported in double-blind trials. In a study versus citalopram, there was a significant difference in reduction of the HAM-A in favor of mirtazapine at week 2 ($p \leq .05$).[8] Two other studies revealed differences in reduction of the HAM-D anxiety/somatization factor in favor of mirtazapine versus paroxetine ($p < .05$ at weeks 1, 3, 4, and 6) and fluoxetine ($p = .196$).[9,25] Similarly, a pooled analysis showed that mirtazapine treatment yielded more HAM-D anxiety/somatization factor responders at weeks 1, 2, and 4 than fluoxetine and paroxetine ($p \leq .05$) (data on file, NV Organon). In a different pooled analysis, HAM-A remission rates were significantly better for mirtazapine versus citalopram/paroxetine at weeks 2, 3, and 4 ($p \leq .05$) (Figure 4).[26] Such rapid improvements in anxiety symptoms with mirtazapine would prove particularly advantageous in patients with comorbid anxiety. Prescription of mirtazapine in these patients may minimize polypharmacy (e.g., concomitant use of benzodiazepines) in initial treatment with SSRIs.

Sleep disturbances are another major aspect of depression, with insomnia occurring in over 90% of depressed patients, highlighted Dr. Hirschfeld. By enhancing daytime functioning and quality of life, it is believed that relieving insomnia early in depression may improve compliance and, ultimately, patients' prognosis.[27] Because stimulation of postsynaptic 5-HT_2 receptors results in sleep disturbances, some antidepressants, such as SSRIs, have an adverse effect on sleep.[28,29] However, drugs that block 5-HT_2 receptors, such as mirtazapine and nefazodone, are likely to contribute to the return of normal sleep. Dr. Hirschfeld presented data from an open-label study of mirtazapine, which evaluated sleep using polysomnographic recordings taken at regular intervals. This study demonstrated sustained significant improvements in sleep efficiency with mirtazapine (86% vs. 70% at baseline; $p < .05$) (Figure 5).[30] Furthermore, mirtazapine significantly decreased night awakenings, increased slow wave sleep, and extended REM latency versus baseline ($p < .05$). These results strongly support the findings of a previous study using polysomnographic recordings.[31] Throughout an 8-week, double-blind study versus venlafaxine, the reduction from baseline on the HAM-D factor IV (sleep disturbance) was significantly larger with mirtazapine from week 1 until the end of the treatment period ($p < .05$). This provides evidence that blockade of the 5-HT_2 receptors by mirtazapine helps to improve sleep architecture.

Depressed patients often experience sexual dysfunction, which is a major cause of treatment discontinuation, increasing the risk of relapse and recurrence.[32] However, it should be noted that patients do not complain about sexual dysfunction unless directly questioned by their doctor, highlighted Dr. Hirschfeld. Treatment-emergent sexual dysfunction is frequent with most antidepressants, including the TCAs, MAOIs, and SSRIs.[33] However, reports of sexual dysfunction with bupropion (3%), nefazodone (≤ 1%), and mirtazapine (< 1%) are rare in both clinical practice and clinical trials. In fact, mirtazapine may improve drug-induced sexual dysfunction, which can be attributed to 5-HT_2 receptor blockade. Six weeks after depressed patients with SSRI-induced sexual dysfunction were openly switched from an SSRI to mirtazapine, 75% reported a return to normal sexual functioning, and 15% experienced a significant improvement from baseline.[34] Also, in an open-label study, mirtazapine exerted beneficial effects on sexual functioning, more prominently in females than males.[35] Indeed, increases of 10% to 52% were observed in measures of desire, arousal, and orgasm. The lack of sexual side effects with mirtazapine is important for patient acceptability, as sexual dysfunction is a major cause of treatment discontinuation.

Depression is associated with a spectrum of key symptoms, including mood, retardation, sleep disturbances, sexual dysfunction, and anxiety, which need to be considered to achieve optimal management of depressed patients. From the data presented, mirtazapine appears to have strong anxiolytic ef-

Figure 5. The Effect of Mirtazapine on Sleep Efficiency[a]



[a]Data from Schittecatte et al.[30] Sleep efficiency = (total sleep time/time in bed) × 100.
*p < .05 vs. baseline.

fects, rapid improvement of sleep, and no sexual side effects. Furthermore, beneficial effects on retardation have been observed with mirtazapine, noted Dr. Hirschfeld. In the pooled data versus fluoxetine and paroxetine, mirtazapine consistently yielded higher responder rates (defined by ≥ 50% reduction) on the HAM-D factor V, psychomotor retardation; statistical significance was reached at week 1 ($p \leq .05$) (data on file, NV Organon). Hence, mirtazapine exhibits early relief of a broad range of core symptoms of depression, facilitating its use in many different patients. ❑

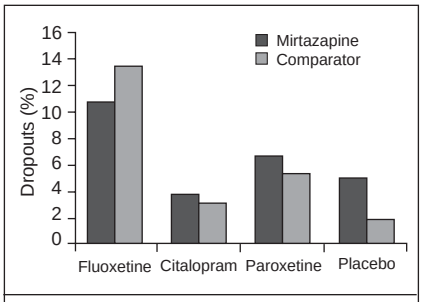
The Tolerability and Safety of Antidepressants

Dr. Steven P. Roose began his presentation by explaining that, given the broad range of efficacious antidepressants now available, the side effect profile is often the critical variable when selecting a drug for a particular patient. Side effects can result from stimulation of the postsynaptic serotonin receptors: 5-HT_{2A} stimulation causes insomnia, anxiety, and sexual dysfunction; 5-HT_{2C} stimulation results in irritability and decreased appetite; and 5-HT_3 stimulation can cause nausea, vomiting, and headache. Noradrenergic receptor stimulation can cause tachycardia, blood pressure effects, dry mouth, and sweating. Blockade of muscarinic, histaminergic, and postsynaptic α_1-adrenergic receptors can induce dry mouth, sedation, and postural hypotension. Side effects can have a major impact on treatment compliance, which is a complex issue affected by multiple factors.

SSRIs stimulate all postsynaptic serotonin receptors, so the expected, and observed, side effect profile common to this class of medication includes nausea, vomiting, headache, insomnia, and sexual dysfunction. At low doses, the SNRI venlafaxine is mainly a serotonin reuptake inhibitor and is, therefore, associated with the serotonergic side effect profile similar to the SSRIs. At high doses, venlafaxine also inhibits norepinephrine reuptake, and this can potentially result in additional side effects such as increased blood pressure. Mirtazapine has a direct effect on noradrenergic neurons and an indirect effect on serotonergic cell firing. Selective blockade of the postsynaptic 5-HT_2 and 5-HT_3 receptors with mirtazapine, preventing occurrence of serotonergic side effects, and histamine receptor blockade result in a distinct side effect profile. Clinical trials comparing mirtazapine with SSRIs show that both drugs are equally well tolerated with respect to dropout rate, even though the side effect profiles were different, noted Dr. Roose (Figure 6).[7–9,36] Patients treated with citalopram or paroxetine experienced more nausea and sexual dysfunction, whereas mirtazapine-treated patients experienced increased appetite and weight gain more often. These side effects of mirtazapine presumably result from blockade of the histamine receptor. Reports of drowsiness and sedation were not significantly different.[8,9] Clinical trial data suggest that sedation is minimized with a starting dose of 30 mg/day. Results from a long-term study have indicated that the proportion of patients with ≥ 7% weight gain was 22% for amitriptyline, 12.7% for mirtazapine, and 3.6% for placebo.[37]

In terms of safety, data from over 4 million patients treated to date have revealed no evidence to indicate that mirtazapine induces significant cardiovascular effects, such as quinidine-like actions or changes in blood pressure or heart rate. However, mirtazapine has not been specifically tested in depressed patients with preexisting cardiovascular disease.

Figure 6. Tolerability of Mirtazapine vs. SSRIs: Drug-Related Dropouts Due to Adverse Events[a]



[a]Data from Wheatley et al.,[7] Kasper,[36] Benkert et al.,[9] and Leinonen et al.[8]

Mirtazapine does not affect the cytochrome P450 system, which implies that the use of mirtazapine with other medications will not result in drug-drug interactions; this is particularly important when treating patients with comorbidity who require concomitant medication, such as the elderly.

To date, 45 cases of mirtazapine overdose have been reported. Patients who had taken an overdose of mirtazapine alone, up to 1500 mg, experienced only minor symptoms, such as somnolence and dizziness, and made a full recovery. Only 5 fatalities have been reported, all mixed overdoses with alcohol, benzodiazepines, or a second antidepressant (most often a TCA); this rate is consistent with previous data on overdose with SSRIs, in which fatalities occur almost exclusively in patients who have taken mixed overdoses.

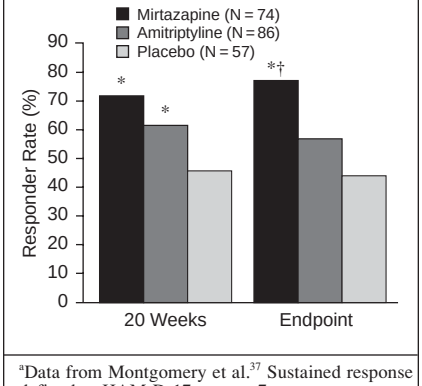
In summary, mirtazapine is notable in that it has repeatedly demonstrated a side effect profile different from that of the SSRIs but comparable safety. Tolerability is a key factor affecting patient compliance with medication; other major variables that can contribute to patient compliance are early and sustained relief of depressive symptoms and ease of use. Compliance depends not only on the medication being taken but also on who is taking the medication, i.e., the patient's conscious attitudes and unconscious fantasies

toward medication and illness. Dr. Roose concluded that physician awareness of these dimensions can contribute to a more effective doctor-patient relationship, resulting in increased medication compliance and, therefore, more effective long-term treatment of depression. ❑

Long-Term Management of Depression

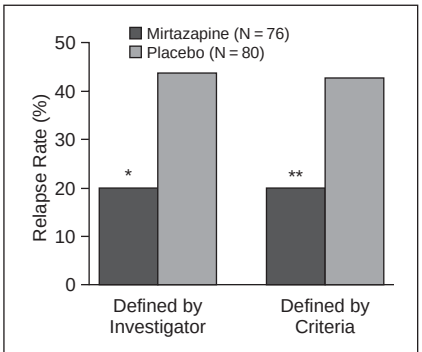
As unipolar major depression is frequently of long duration and associated with a high probability of recurrence, antidepressants must exhibit sustained efficacy. To demonstrate the long-term efficacy of mirtazapine, Dr. Martin B. Keller summarized recent studies. In a meta-analysis of 4 double-blind, placebo-controlled trials in which patients were treated for up to 2 years, mirtazapine exhibited sustained superior efficacy compared with amitriptyline (Figure 7).[37] Remission rates were significantly higher (p = .008) and fewer patients had 1 or more adverse events (p = .001) with mirtazapine than with amitriptyline. In long-term extensions of trials versus the SSRIs (citalopram and paroxetine), mirtazapine demonstrated strong and sustained efficacy at least equal to the SSRIs (data on file, NV Organon). Proportions of long-term responders and remitters were high for all agents.

Figure 7. Sustained Response With Mirtazapine vs. Amitriptyline in Long-Term Treatment[a]



[a]Data from Montgomery et al.[37] Sustained response defined as HAM-D-17 score ≤ 7.
*p ≤ .05 vs. placebo.
†p ≤ .05 vs. amitriptyline.

Figure 8. Mirtazapine in Relapse Prevention[a]



[a]Data from Thase et al.[38]
*p = .001 vs. placebo.
**p = .002 vs. placebo.

Relapse rates in depressed patients on long-term, maintenance therapy are unacceptably high, noted Dr. Keller. However, some of the newer antidepressants may have improved effectiveness in preventing relapse. Relapse data have been obtained from a long-term, double-blind, placebo-controlled trial of mirtazapine (data on file, NV Organon). The overall relapse rate of 19.7% for mirtazapine-treated patients was significantly lower than for placebo as defined by the investigator's clinical judgment (43.8%; p = .001) and by the criteria of HAM-D score ≥ 18 at a single visit or 15–17 at 2 consecutive visits (42.5%; p = .002) (Figure 8).[38] In addition, mean time to relapse was longer with mirtazapine (71.9 vs. 52.5 days). Hence, it appears that mirtazapine has strong beneficial effects not only in short-term efficacy but also in long-term efficacy and prevention of relapse. Dr. Keller highlighted that use of antidepressants with persistent efficacy is important in the management of depression, particularly in patients who require maintenance therapy. ❑

Conclusions

Substantial progress in the management of depression has been made over the last 15 years. This is largely due to the introduction of antidepressants with similar efficacy but also improved tolerability compared with the TCAs. However, variations in effectiveness, onset of action, and potential for side effects have been observed across the different classes of antidepressants, which could be explained by their pharmacologic mechanisms. Much evidence indicates that dual-acting drugs such as mirtazapine and high-dose venlafaxine—which act on both serotonin and norepinephrine—may be more effective against depression than single-acting drugs. Recent studies have shown that new dual-action antidepressants are as effective as the TCAs, but have the added benefit of fewer side effects and safety in overdose. Moreover, in the first comparative study versus venlafaxine, mirtazapine demonstrated at least equal efficacy and better tolerability.

Mirtazapine has a unique mode of action, resulting in an immediate and persistent increase in serotonergic cell firing, which is presumably responsible for the fast onset of action. This advantage has been observed in a number of studies comparing mirtazapine with SSRIs, and preliminary pattern analysis and survival analysis have provided further support—the overall effect is a clinically relevant, rapid reduction in depressive syndrome. Mirtazapine has been shown to improve core symptoms of depression, including anxiety, sleep disturbances, somatization, and sexual dysfunction, which can be left untreated or worsened by other antidepressant drugs. Early relief of this wide range of symptoms, combined with good tolerability, will make it easier for patients to accept treatment and may ultimately result in improved clinical

outcome. Furthermore, mirtazapine is effective in all types of depressed patients, including those with severe illness.

Long-term efficacy of antidepressants is also crucial for maximizing patients' outcome and for the prevention of relapse and recurrence. There is convincing evidence that mirtazapine has strong and sustained efficacy; indeed, mirtazapine has yielded superior rates of remitters compared with amitriptyline. In addition, data accumulated so far indicate that mirtazapine is effective in relapse prevention.

Antidepressants vary considerably in their propensity for side effects and safety, which can be explained by their pharmacology. Mirtazapine specifically blocks 5-HT_2 and 5-HT_3 receptors, reducing the incidence of the serotonergic side effects commonly seen with the SSRIs (e.g., nausea, vomiting). However, weight gain and increased appetite are reported more frequently with mirtazapine than with other antidepressants, which can probably be attributed to its antihistaminergic effect. Blockade of 5-HT_2 receptors with drugs such as mirtazapine and nefazodone also results in rapid and persistent beneficial effects on both sleep and anxiety in depressed patients. This is in contrast to the SSRIs, which can exacerbate anxiety early in treatment and have detrimental effects on sleep architecture.

Data from over 4 million patients have shown that mirtazapine is safe in overdose and does not cause quinidine-like (e.g., cardiac conduction disturbance) or vital sign changes (e.g., change in heart rate). No clinically meaningful interaction with the cytochrome P450 system means mirtazapine can easily be used with concomitant medication; this is especially important in elderly patients.

Mirtazapine has demonstrated broad efficacy, good tolerability, and rapid onset of action in all depressed patients. These are key attributes for an easy-to-use, successful antidepressant agent, but the most effective and tolerable medication will not work unless patients are compliant. Hence, to achieve optimal short- and long-term management, doctors need to combine efficacious and well-tolerated medication with a good patient-doctor therapeutic alliance. ❑

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Expert Meeting and Presenters

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