Mirtazapine: Other Indications

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During the last decade, it became evident that antidepressants may represent a useful treatment option for a variety of primary psychiatric disorders other than depression. Improved understanding of both underlying etiology of these disorders and pharmacologic modes of action of available treatments has led to an improvement in conditions such as panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and premenstrual dysphoric disorder. In addition, evidence is accumulating that some new antidepressants may be of therapeutic value in treatment of some subtypes of depressive disorder previously unresponsive to treatment or difficult to treat, such as seasonal affective disorder, depression with atypical features, and recurrent brief depression. Mirtazapine is an antidepressant with mode of action different from other currently available antidepressants. A review of currently available data of mirtazapine's use in indications other than depression and in some types of depressive disorder is presented.

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Over the last decade, it has become clear that antidepressant agents may have a role in the treatment of a range of psychiatric disorders other than depression, such as panic disorder, generalized anxiety disorder, and posttraumatic stress disorder (PTSD). Furthermore, depression is often comorbid with one or more of these types of psychiatric disorders. In a United States study, over 60% of patients affected by a psychiatric disorder suffered from more than one disorder.[1] In addition, there are subtypes of depression, such as recurrent brief depression, atypical depression, and menopausal depression, that are difficult to treat using conventional antidepressants, but that may benefit from treatment using the latest antidepressants, which have different modes of action.

It is thought that serotonin (5-HT) has a role in both depressive and anxiety disorders. Whereas evidence suggests that 5-HT_{1A} receptor function is impaired in depression, excessive activation of serotonin pathways is possible in panic and generalized anxiety disorders.[2] It is therefore likely that antidepressants that modulate serotonin function may be effective in both these conditions. Mirtazapine is a novel antidepressant that has a unique dual mode of action. Known as a noradrenergic and specific serotonergic antidepressant (NaSSA), its antagonist action increases the release of both norepinephrine and serotonin, enhancing noradrenergic and serotonergic neurotransmission. However, it also potently blocks 5-HT_2 and 5-HT_3 receptors. The excellent efficacy and safety of mirtazapine have been established in major depression in over 1 million patients, and it has been shown to be at least as effective as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) in these patients.[3–5] Recent research has demonstrated that mirtazapine also shows promise in a number of nondepressive psychiatric disorders and in some difficult-to-treat subtypes of depression.

ANXIETY DISORDERS

Anxiety disorders are common in the general public, frequently made worse by their comorbidity with depression. There are a number of types of anxiety disorders, such as panic disorder, specific phobias, social phobia, PTSD, obsessive-compulsive disorder, and generalized anxiety disorder.

Panic Disorder

Panic disorder is a chronic, debilitating condition that typically first occurs in older teenagers or individuals aged 20 to 25 years and consists of repeated panic attacks and severe anxiety. It affects over 3 million patients in the United States. It may be triggered by a life event, but the predisposition to panic disorder is inherited and the condition might worsen as the patient ages if it is not treated.

A panic attack is characterized by a range of symptoms, including breathing difficulties, dizziness, nausea, and shaking, accompanied by an overwhelming feeling of doom (Table 1). Treatment of panic disorder can alleviate panic attacks in 70% to 90% of those who experience them, although early treatment is most effective. Even after a

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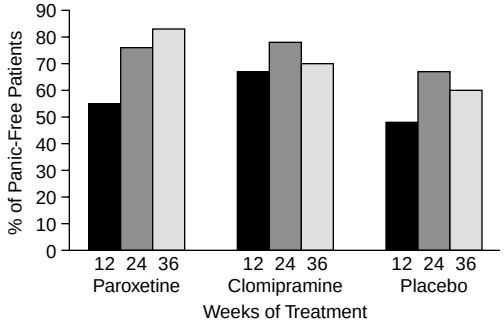
Table 1. Symptoms of a Panic Attack

Unsteadiness/dizziness
Shortness of breath/feelings of choking
Palpitations/tachycardia
Trembling/shaking
Nausea/abdominal disturbances
Sweating/flushes/chills
Paresthesia
Chest pain
Depersonalization
Fear of losing control
Fear of dying/feelings of doom

Figure 1. Proportion of Panic-Free Patients After 12, 24, and 36 Weeks' Treatment With Paroxetine, Clomipramine, or Placebo[a]



[a]Adapted from reference 6, with permission.

relapse, treatment for panic disorder can be effective. It has been demonstrated that panic disorder benefits from long-term treatment, as it is a chronic, recurrent condition.[6] In addition, panic disorder is frequently comorbid with depression, and, to be effective, any treatment option needs to reflect this.[7] However, only 1 in 3 patients receive appropriate treatment for panic disorders.

While serotonin undoubtedly plays a major role in the pathogenesis of panic disorder, its exact function is unclear.[8] Evidence points toward either an excess or a deficit of serotonin being responsible for panic disorder; clearly, serotonergic dysfunction is involved. Treatment of panic disorder with SSRIs is effective, and the proportion of patients who are panic-free improves with continued treatment (Figure 1). Another treatment option for panic disorder is benzodiazepines, but their use is associated with dependency problems.

Recently, a study was conducted to determine the efficacy of the NaSSA mirtazapine in panic disorder. Patients with DSM-IV diagnosed panic disorder received mirtazapine for 12 weeks, and a reduction in the number and intensity of panic attacks was observed in a preliminary analysis (data on file, NV Organon, 1999).

Posttraumatic Stress Disorder

PTSD is a pathologic response by people who have experienced or witnessed a traumatic event for which they are not prepared, such as military combat, a serious car or plane accident, a terrorist attack, or physical assault such as rape. The common thread is that the individual was exposed to actual or threatened death or serious injury and responded with intense fear, helplessness, or horror. Individuals with PTSD will reexperience the event and persistently avoid stimuli associated with the event. They experience a numbing of general responsiveness coupled with increased arousal. To be termed as PTSD, a patient's condition must last for at least 1 month.[9]

Approximately 30% of the general population will be exposed to an event capable of producing PTSD in their lifetime, but only 10% to 20% of these individuals will develop PTSD.[9] Thus, the prevalence of PTSD in the general population is estimated to be between 3% and 6%. PTSD is associated with increased rates of other psychiatric complaints, and between 80% and 83% of PTSD patients have or develop comorbid psychiatric illnesses.[10] PTSD is a chronic disease, and over 40% of patients will still have PTSD 10 years after the initial trauma was experienced. Although PTSD can spontaneously improve without treatment, this is only likely in the first year of the condition. However, with treatment, the duration of PTSD can be shortened.

There are a number of treatment options for PTSD. Studies involving TCA treatment have produced disappointing results. In one study, in which 46 war veterans with PTSD received amitriptyline for up to 8 weeks, 64% of the recipients were still diagnosed with PTSD at the end of treatment.[11] Similarly, in a study in which 18 war veterans with PTSD received desipramine for 4 weeks, the PTSD symptoms did not respond to treatment, although underlying depression was alleviated.[12] The reversible inhibitor of monoamine oxidase-A (RIMA) moclobemide has shown favorable results in patients with PTSD.[13] However, controlled, double-blind studies are required to confirm these results. Moreover, although it is claimed that moclobemide treatment is safer than that with standard monoamine oxidase inhibitors (MAOIs), there is still a risk of drug interactions, and restrictions to control the dietary intake of tyramine are required. These limitations may restrict the use of moclobemide in PTSD.

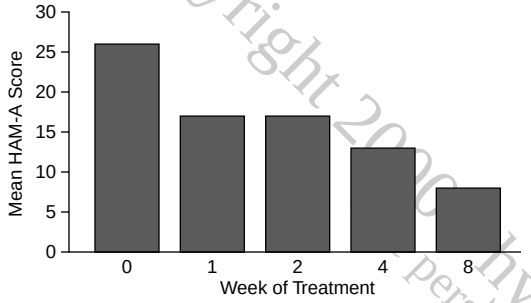
There has been much research into the efficacy of SSRIs in PTSD.[10] An open study was conducted in 20 Vietnam war veterans who received fluoxetine for up to 48 weeks.[14] Sixty-five percent of patients experienced a 50% or better reduction in baseline Clinical Global Impressions (CGI) scale scores. A separate study involving Vietnam veterans also demonstrated the beneficial effects of fluoxetine on explosive outbursts of rage and impulsive actions.[15] In another open study of fluoxetine, PTSD patients experienced significant improvements in PTSD scores, although most improvement occurred after 6 weeks of treat-

Table 2. Change From Baseline PTSD Scores in Patients Treated With Mirtazapine[a]

Scale	All patients (N = 6)	Responders (N = 3)
Structured Interview for PTSD	–9.2	–15.7
Short PTSD Rating Interview	–8.7	–14.0
Davidson Trauma Scale	–26.5	–43.0
MADRS	–6.4	–12.8

[a]Data from reference 23. Abbreviations:
MADRS = Montgomery-Asberg Depression Rating Scale,
PTSD = posttraumatic stress disorder.

Figure 2. Mean Hamilton Rating Scale for Anxiety (HAM-A) Scores in Patients With Generalized Anxiety Disorder Treated With Mirtazapine[a]



[a]Data from reference 24. Significant improvement from week 0 scores seen from week 1 onward ($p < .02$).

ment.[16] These results were confirmed by a placebo-controlled, double-blind study in which 33 PTSD patients received fluoxetine for 5 weeks.[17] The SSRIs fluvoxamine and sertraline have also shown benefits in PTSD.[18–21] However, the benefits of SSRI treatment in these patients were sometimes limited by undesirable side effects.

A 12-week open study of nefazodone, which has potent 5-HT_2 receptor blocker activity and also inhibits 5-HT and norepinephrine reuptake, was conducted in 17 patients with PTSD.[22] Significant improvements in PTSD scores were observed, and 43% of patients responded to treatment, although a high proportion (N = 8) failed to complete the study. These results need to be confirmed by a placebo-controlled, double-blind study. Recently, the NaSSA mirtazapine showed promising results in a pilot study conducted in 6 patients with severe, chronic PTSD.[23] After 8 weeks' treatment, 50% of patients experienced a 50% or better improvement in PTSD scores. Improvements were noted in both interviewer-administrated and self-rated scales (Table 2).

Generalized Anxiety Disorder

Mirtazapine has also been shown to be effective in generalized anxiety disorder. An 8-week, open pilot study was conducted in 10 patients with major depression and generalized anxiety disorder.[24] There were significant progressive improvements in both depression and anxiety scores (Figure 2) throughout treatment.

Table 3. Characteristics of Brief Recurrent Depression and Dysthymia[a]

Brief Recurrent Depression
Subthreshold duration (3–4 d)
Associated with impairment and distress
Assessment and definition problems
20 episodes/y at 18-d intervals
Effectively ill 17% of time
2:1 female:male sufferers
Prevalence high (10%)
Dysthymia
Confused with major depression
Heterogeneity of onset, course, and comorbidity
Early/late onset
Primary/secondary illness
Double depression
Atypical depression

[a]Data from reference 25.

DEPRESSIVE DISORDERS

Some subtypes of depression, such as brief recurrent depression, can be difficult to treat using conventional antidepressant therapies. Mirtazapine has shown promising efficacy in a number of types of depression other than major depression.

Brief Recurrent Depression

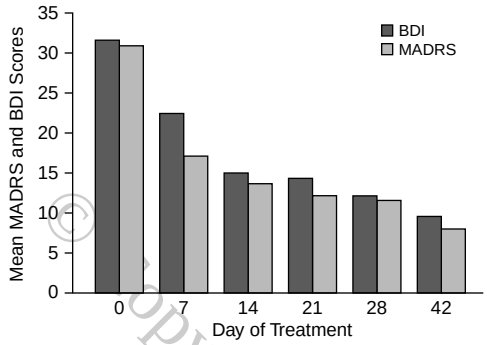
Recurrent brief depression consists of repeated depressive episodes that are as severe as major depression but of shorter duration (Table 3). Episodes are 3 to 4 days long and occur roughly every 18 days.[25] The prevalence of brief recurrent depression is approximately 10%. There are many methodological issues regarding the investigation of treatments for brief recurrent depression that have yet to be resolved, and few such studies have been conducted.

Studies in brief recurrent depression have not demonstrated any superiority for SSRIs over placebo, and it is possible that a dual mechanism of action may be required to effectively treat this condition.[26,27] Mirtazapine has a dual action and may therefore be effective in brief recurrent depression. In 2 patients with brief recurrent depression who were treated with mirtazapine for 4 months, there were marked reductions in the severity, duration, and frequency of the depressive episodes.[28] These promising results need to be followed up by a controlled study.

Dysthymia

The diagnosis of dysthymia is controversial.[25] It is similar to major depression but distinguished from it by being less severe but more chronic (Table 3), but, in the case of double depression, the 2 conditions can overlap. It covers a heterogeneous group of patients, some of whom develop the condition early in life and some in whom it occurs

Figure 3. Mean MADRS and Beck Depression Inventory (BDI) Scores in Patients With Menopausal Depression Treated With Mirtazapine[a]



[a]Data from reference 30.

much later. There is evidence that mirtazapine may be effective in dysthymia. In an open study, 15 patients with dysthymia received mirtazapine for up to 10 weeks.[29] Significant improvements were observed according to Hamilton Rating Scale for Depression and Beck Depression Inventory (BDI) scores, and mirtazapine was well tolerated. These promising results warrant further investigation.

Menopausal Depression

Depression occurs in 14% to 20% of women during menopause, and perimenopause is the time when 35% of women experience depression for the first time. An open study was conducted in 20 menopausal women with major depression, the majority of whom (90%) were resistant to SSRI treatment.[30] During 6 weeks' treatment with mirtazapine, there were progressive improvements in depression as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) and the BDI (Figure 3). Twenty-five percent of patients responded to treatment by day 7, and by the beginning of the third week of treatment, 50% of patients had achieved a 50% reduction in MADRS scores. The main improvements were in sleeping patterns and appetite, but patients also reported improvements in menopausal symptoms such as anxiety, insomnia, and sweating.[30]

CONCLUSIONS

Mirtazapine is an antidepressant with a novel, dual mode of action that affects the neurotransmission of both norepinephrine and serotonin. There are a range of anxiety-related and difficult-to-treat depressive conditions that may benefit from mirtazapine including panic disorder, PTSD, generalized anxiety disorder, brief recurrent depression, dysthymic disorder, and menopausal depression. Further studies with mirtazapine in these indications seem warranted.

Drug names: amitriptyline (Elavil and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft).

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