A Trilogy Case Review Highlighting the Clinical and Pharmacologic Applications of Mirtazapine in Reducing Polypharmacy for Anxiety, Agitation, Insomnia, Depression, and Sexual Dysfunction

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Background: Mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA), is characterized by a unique receptor-specific pharmacologic profile and tolerable side-effect profile in comparison to other antidepressants. It has been reported to have a low incidence of agitation, anxiety, and insomnia, which may be due to blockade of 5-HT_2 and 5-HT_3 receptors. This unique multireceptor-mediated clinical pharmacologic profile may reduce the need for polypharmacy in selected patients.

Case reports: Three cases are presented. In case 1, mirtazapine was able to rapidly treat anxiety and agitation in a 90-year-old woman. This was confirmed with 3 consecutive challenges with mirtazapine. In case 2, both a mood disorder and insomnia were successfully treated with rapid resolution in a patient by using mirtazapine. In case 3, the patient experienced sexual dysfunction while receiving sertraline and developed insomnia with the addition of bupropion. The addition of mirtazapine and the discontinuation of sertraline and bupropion resolved the sexual dysfunction and insomnia. Polypharmacy interventions were decreased in these patients through receptor-specific events from mirtazapine.

Conclusion: The new antidepressant mirtazapine appears to be an effective strategy for treating anxiety, agitation, and insomnia and for diminishing SSRI-related sexual dysfunction without compromising the patient's therapeutic response to the medication while decreasing the need for additional pharmacotherapies. More than 70% of patients with major depression will have anxiety symptoms. The 5-HT_2 receptor seems to play a major role in the regulation of anxiety. The anxiolytic properties of mirtazapine may be due to its antagonism of 5-HT_2 receptors and can appear as early as the first week of treatment.

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Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA). This dual action antidepressant increases both norepinephrine (NE) and serotonin (5-HT) concentrations and acts as a potent 5-HT_2 and 5-HT_3 antagonist with low affinity for 5-HT_1 receptors. In addition, mirtazapine has presynaptic α_2-autoantagonistic and heteroantagonistic properties. Unlike selective serotonin reuptake inhibitors (SSRIs), it has been reported to have a low incidence of agitation, anxiety, insomnia, and sexual dysfunction.[1,2] Since agitation, anxiety, insomnia, and sexual side effects are believed to be mediated through 5-HT_2 (2C in the choroid plexus, 2A in the cortex and basal ganglia) and 5-HT_3 (peripheral, autonomic, and central nervous system) stimulation, possible relief of symptoms may result from blocking these specific receptors with mirtazapine.[3] Antagonism of 5-HT_3 is also associated with antiemetic effects. The minimal agonistic effects at 5-HT_1 receptors and the blockade at 5-HT_2 receptors may further reduce the risk of serotonin syndrome and explain the anxiolytic properties of mirtazapine.[4–6] Three serotonin receptors are thought to be involved in the regulation of anxiety (decreased stimulation with 5-HT_{1A}, increased stimulation with 5-HT_2, increased stimulation with 5-HT_3).[7] Receptor antagonism is also described at the H_1 receptor.

Antidepressants are commonly used to treat anxiety and insomnia and may have adverse as well as clinical effects.[8,9] Akathisia, restlessness, anxiety, agitation, jitteriness, and insomnia have been reported in patients taking tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and SSRIs, while benzodiazepines may cause mental status changes, aggression, loss of control, amnestic effects, and disinhibition.[7–12] Patients taking

SSRIs may require additional medication for sleep. Mirtazapine is an antidepressant that may not only minimize the risk of treatment-emergent anxiety, insomnia, and agitation, but also relieve both anxiety and insomnia in depressed patients, perhaps through the specific blockade of 5-HT_2 and H_1 receptors.[1,13] Mirtazapine's potential value in treating anxiety has been evaluated. The efficacy of mirtazapine, 15 to 25 mg/day, in anxiety was evaluated in 40 patients.[13] Anxiety symptoms were assessed using the Hamilton Rating Scale for Anxiety, the Zung Anxiety Scale, and the Global Assessment Scale. Mirtazapine-treated patients experienced significantly greater improvements from baseline in overall anxiety symptoms, psychic anxiety, and global functioning than placebo-treated patients.

Sexual dysfunction is known to be caused by both depression and antidepressants, especially those with increased serotonergic activity via 5-HT_2 stimulation.[13] The incidence of sexual dysfunction with SSRIs ranges from 2% (fluoxetine) to 40% (sertraline, paroxetine) as reported in package inserts and published data, while higher incidences have been reported in clinical practice.[14,15] Antidepressants such as mirtazapine enhance serotonergic transmission and may offer a viable therapeutic option for patients with sexual dysfunction.[15,16] Relief of SSRI-induced sexual dysfunction has been demonstrated with mirtazapine.[17,18]

Based on U.S. clinical trials, the dose of mirtazapine is titrated upward over a range of 15 to 45 mg/day, depending on the response to treatment. For the treatment of depression, the recommended starting dose is 15 mg, given at bedtime. The mean final doses in short-term U.S. clinical trials with outpatients were primarily in the 20- to 25-mg/day range.[19] Although separate clinical entities, anxiety and depression are amalgamated in the major proportion of patients presenting in clinical practice. Anxiety symptoms include worry, psychic anxiety, somatic anxiety, panic attacks, and phobic symptoms. Somatic anxiety symptoms may be similar to somatic depressive symptoms (chest pain, fatigue, cephalalgia, insomnia, abdominal pain). Selecting effective and efficient pharmacotherapy focused at relief of both the presenting anxiety symptoms and depression is a therapeutic collaboration between the clinician and the patient.

The presence of anxiety symptoms in patients diagnosed as having depression appears to be an important factor in the clinical management of major depression and may serve as a clinician's guide to selection among the available antidepressants.[20] Greater than 70% of patients with depression have symptoms of anxiety, mainly represented by worry and psychic anxiety,[21] and 20% to 40% have a somatic anxiety, panic attacks, or phobic symptoms.[21] Depressed patients who have higher ratings for anxiety are more severely ill, take longer to recover, and demonstrate a less than adequate response to antidepressants.[21,22] Recent evidence suggests that the presence of severe anxiety is a predictor of suicide in depressed patients.[23]

A meta-analysis of 8 randomized, double-blind, placebo-controlled clinical trials of 6 weeks' duration was conducted to assess the efficacy of mirtazapine in comparison with placebo for the relief of depression in patients with symptoms of anxiety.[8] This meta-analysis utilized the mean improvement from baseline scores for the Hamilton Rating Scale for Depression factor score 1 (anxiety/somatization), which refers to the sum of items 10, 11, 12, 13, 15, and 17. This last-observation-carried-forward (LOCF) analysis of all treated patients with a post-baseline evaluation demonstrated a statistically significant reduction in anxiety/somatization score with mirtazapine early and consistently throughout treatment, from week 1 through 6 compared with placebo. The study design excluded concomitant anxiolytic agents any time during the trials.

The following series of 3 case reviews describes patients treated with mirtazapine because of agitation, anxiety, insomnia, or sexual dysfunction, and in part based on the unique receptor-specific pharmacologic function of mirtazapine.

CASES

Case 1

A 90-year-old woman with a past medical history significant for coronary artery disease, coronary artery bypass graft, and right hip wound secondary to hip surgery was receiving 1 tablet of hydrocodone 2.5 mg/acetaminophen 250 mg combination every 4 to 6 hours as needed; digoxin, 0.125 mg q.d.; and docusate sodium. The patient experienced abrupt mental status changes including screaming, yelling, and inability to communicate effectively on entry to the unit. Her changes in mental status could have been caused by a number of etiologies including multiple medical problems coupled with changes in surroundings and surgery.

Opiates were discontinued, and the patient was placed on mirtazapine, 7.5 mg at 8:30 p.m.; gabapentin, 100 mg every 12 hours; and tramadol, 25 mg every 6 hours. She was monitored both subjectively and objectively; the screaming and yelling decreased within 4 hours of the first dose of mirtazapine, 7.5 mg. The patient's outbursts reemerged when mirtazapine therapy was discontinued. These changes were noted with 3 consecutive challenges and reinstitution of mirtazapine. The modulation of a calming action was noted to be rapid. The patient continued to receive gabapentin and tramadol to control her pain.

Case 2

A 47-year-old woman presented with a primary complaint of insomnia. Past medical history revealed dysthy-

mia, long-term insomnia, daytime fatigue, and difficulty driving home after work. She self-medicated with over-the-counter drugs such as doxylamine succinate and diphenhydramine in combination with acetaminophen, which she discontinued because of side effects and only transient improvement in sleep. Several different benzodiazepines (i.e., clonazepam, diazepam, lorazepam) were prescribed; however, she complained of worsening depression, excessive somnolence, and impaired intellectual function and memory deficits. Secondly, the patient experienced rebound insomnia with paradoxical reactions such as disinhibition, agitation, psychosis, and increased anxiety-like symptoms.

The patient was tapered off the benzodiazepine regimen, and zolpidem, 20 mg at bedtime, was initiated with only short-term relief of insomnia. She was reevaluated and placed on a strict caffeine-free diet, appropriate sleep hygiene principles were taught, and mirtazapine, 7.5 mg 1 hour before bedtime with a repeat dose of 7.5 mg if awake between the hours of 1 a.m. to 4 a.m., was prescribed. On the basis of the patient's satisfaction, the physician increased her dose to 15 mg at 8:30 p.m. for an approximate sleep time of 10 p.m. The patient reported a rapid restoration of her sleep patterns, lack of daytime sedation, and improved affect. Subsequently, her dosage was increased to 45 mg/day with resolution of dysthymia.

Case 3

A 36-year-old man suffered from 4 episodes of depressive illness within a 3-year period. The patient was prescribed sertraline, 50 mg/day, with the dose titrated to 200 mg/day. During this time (12 weeks), he reported headache, insomnia, nausea, anxiety, and loose stools to his psychiatrist. Because of these complaints, he subsequently visited his primary care physician, who prescribed amitriptyline, 25 mg to 50 mg, for his insomnia without knowing that the patient was already being treated for depression (due to the patient's nondisclosure of this management and diagnosis). The patient then developed fever, diaphoresis, and hyperreflexia and was diagnosed with serotonin syndrome by his primary care physician who uncovered by investigation that he was concurrently taking both agents. Both drugs were discontinued, and the patient's symptoms resolved after symptomatic treatment.

Following a 14-day washout period and complete resolution of the serotonin syndrome, the patient was restarted on sertraline, 100 mg/day, which was later titrated to 200 mg/day. Within 15 days of treatment with sertraline, the patient began complaining of sexual dysfunction, characterized by delayed ejaculation and impotence. Bupropion was added to the pharmacotherapy to treat the patient's sexual dysfunction. The patient experienced tachycardia, insomnia, and xerostomia with no change in his sexual dysfunction. Both sertraline and bupropion were discontinued, and mirtazapine, 30 mg/day, was started after a 15-day washout period and titrated to 45 mg.

After 8 days of mirtazapine therapy, he reported restoration in sexual functioning (i.e., he no longer experienced impotence and delayed ejaculation). In addition, the patient reported a rapid improvement in his sleep patterns and anxiety symptoms and an increased ability to concentrate and perform more effectively at work. His mood improved after 2 weeks of mirtazapine therapy, and the patient demonstrated continued improvement of his depression with no significant side effects after 1 year of therapy.

DISCUSSION

These cases provide evidence that mirtazapine can be used to treat agitation, anxiety, insomnia, and SSRI-induced sexual dysfunction and reduce the need for polypharmacy.

In case 1, the patient's symptoms of anxiety/agitation responded rapidly to mirtazapine. Although this patient was not depressed, it is important to note that other studies have evaluated mirtazapine's ability to treat anxiety/agitation symptoms of depression. Meta-analysis and clinical trials[8] have demonstrated that mirtazapine is superior to placebo and comparable to amitriptyline in treating major depression with coexisting symptoms of anxiety/agitation or anxiety/somatization, as discussed earlier. In clinical trials, mirtazapine-treated patients demonstrated statistically significant reductions in symptoms of anxiety/agitation and anxiety/somatization compared with placebo. Improvements in anxiety/agitation and anxiety/somatization symptoms were similar for mirtazapine and amitriptyline throughout the study.[7] Mirtazapine has also been found in one study to be superior to fluoxetine in treating symptoms of anxiety/somatization in depressed patients.[24]

Case 2 describes mirtazapine's role in rapidly treating insomnia in patients with mood disorders. Unlike sedating antidepressants and benzodiazepines, mirtazapine does not appear to affect sleep patterns, cause memory deficits, or leave the patient feeling tired or hungover, nor does long-term use appear to cause tolerance and dependence as is the case with benzodiazepines.[25,26] However, mirtazapine, at low doses, may cause drowsiness in some patients.[27] The results of a pilot, open-label study in patients with sleep disturbances and major depression[25] indicate that mirtazapine is associated with improved sleep. Patients experienced shorter sleep-onset latency, pronounced increase in total sleep time, and marked improvement in sleep efficiency. Similar to patients in this pilot study, the patient in case 2 did not experience daytime sedation, which is often a problem with benzodiazepines and sedating antidepressants.

Lastly, SSRI therapy is known to induce sexual dysfunction in some patients.[14] In case 3, the patient's lack of sexual dysfunction after the addition of mirtazapine is consistent with findings reported in the literature.[16,17] In another pilot study,[16] patients with SSRI-induced sexual dysfunction were switched to mirtazapine. None of the patients reported sexual dysfunction while taking mirtazapine, and all responded to the antidepressant effects of the drug as well. Also, placebo-controlled trials with mirtazapine[2] demonstrated low and similar percentages of sexual dysfunction with mirtazapine and placebo. Further, SSRI sexual dysfunction has been managed by the addition of mirtazapine.[16,18]

Clinicians are often faced with the challenge of finding cost-effective strategies for treating depression, anxiety/agitation, insomnia, and sexual dysfunction without compromising the patient's response to the particular medication and the challenge of decreasing the patient's pharmacologic burden.[19] Mirtazapine appears to be effective in rapidly treating anxiety/agitation and insomnia. The prescribing of mirtazapine may diminish anxiolytic, neuroleptic, sedative, and hypnotic polypharmacy. It does not appear to cause sexual dysfunction and may treat sexual dysfunction caused by other antidepressants. Also, mirtazapine has significantly less CYP450-inhibiting drug interactions than SSRIs or nefazodone.[27] Controlled studies are necessary to fully determine the role of mirtazapine in treating anxiety, agitation, and insomnia as well as serotonin syndrome and SSRI-induced sexual side effects.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), clonazepam (Klonopin and others), diazepam (Valium and others), digoxin (Lanoxin and others), diphenhydramine (Benadryl and others), docusate sodium (Colase and others), doxylamine succinate (Unisom), fluoxetine (Prozac), gabapentin (Neurontin), lorazepam (Ativan and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), tramadol (Ultram), zolpidem (Ambien).

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