

FOR YOUR INFORMATION



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Mirtazapine: a Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)

There are three key neurotransmitter receptor systems [norepinephrine (NE), serotonin (5-hydroxytryptamine; 5-HT) and dopamine (DA)] in the brain that are believed to be involved in the mechanism of antidepressant therapy. The current biological model for depression theorizes that up-regulation of postsynaptic receptors in response to decreased activities in one, two or all of these three neurotransmitter systems results in depression. In fact, every known antidepressant increases neurotransmission of one, two or all of these neurotransmitters and over time, down-regulation of these receptors to their “normal” state occurs. It has been postulated that the time for an antidepressant to down-regulate these receptors may coincide with onset of antidepressant efficacy.

Mirtazapine (Remeron®) is a tetracyclic piperazinoazepine antidepressant, structurally distinct from currently available antidepressants, that increases NE and selectively 5-HT type 1 neuronal firings in the brain by:

1. blocking presynaptic alpha-2 noradrenergic autoreceptors and presynaptic alpha-2 serotonergic heteroreceptors.
2. blocking postsynaptic 5-HT₂ and 5-HT₃ serotonergic neurons.

Pharmacodynamics

The intended effect of mirtazapine (MT) is its ability to produce antidepressant properties and minimize many of the troublesome side effects associated with selective serotonin reuptake inhibitors (SSRIs) such as akathisia, anxiety, insomnia, nausea, vomiting and sexual dysfunction.

The stimulation of 5-HT₂ serotonergic neurotransmission seems to be related to akathisia, anxiety, insomnia and sexual dysfunction; the stimulation of 5-HT₃ serotonergic

neurotransmission seems to be related to nausea. Hence, MT, by its postsynaptic 5-HT₂ and 5-HT₃ blockade, seems to reduce all of these effects. However, the postsynaptic blockade of 5-HT₂, specifically the type 5-HT_{2c}, is implicated in causing weight gain.

Other effects

MT has high antihistaminic type H₁ but low antidopaminergic effects. It also has low antimuscarinic-cholinergic and alpha-1 adrenergic (cardiovascular) effects unlike the tricyclic antidepressants (TCAs).

Comparative Efficacy Trials

The efficacy of MT is established in several prospective, randomized, double-blind trials of 4 to 8 weeks duration with at least 50% reduction in Hamilton Rating Scale for Depression (HAM-D) scores as end points.

TCA

In meta-analysis of five trials comparing MT and amitriptyline, about equal number (70%) of patients responded to both agents. MT has also been compared to clomipramine, doxepin, trazodone and imipramine with equal efficacy.

SSRI

Compared with fluoxetine, paroxetine or citalopram, MT showed equal or slightly better efficacy and a seemingly faster onset of action. Whether or not this faster onset is due to MT's ability to faster down-regulate postsynaptic serotonin and/or norepinephrine receptors is purely speculative at this time. A multi-center study comparing MT to fluoxetine showed that MT was found to be more effective after 3 and 4 weeks of therapy for patients with moderate to severe major depressive disorder. Another

multi-center study comparing MT to paroxetine showed that MT and paroxetine were equally effective in reducing the overall symptoms of depression and anxiety in patients with major depressive episode after 6 weeks of therapy.

Venlafaxine

In one poster presentation, efficacy and tolerability of MT and venlafaxine were compared in hospitalized severely depressed patients with melancholia. Dose increase was faster than usual due to the severity of the illness. Both agents were equally efficacious but more venlafaxine (15.2%) than the MT group (5.1%) discontinued therapy due to adverse events.

Pharmacokinetics

MT displays linear pharmacokinetics over a dose range of 15-80mg/day. Bioavailability (F) of the tablet formulation is 0.5 and it is rapidly and completely absorbed with peak plasma concentration reaching approximately 2 hours following administration. Its volume of distribution (Vd) is 4.5L/Kg and it is 85% plasma protein bound. It is eliminated renally (approximately 75%) and by feces (approximately 15%) with the elimination half-life ranging from 20-40hrs.

It is metabolized by cytochrome P450 (CYP) 1A2, 2C9, 2D6 and 3A3/4 isoenzymes. Hence, any drug that is metabolized by these isoenzymes will influence the plasma levels of MT, or MT may influence plasma levels of concomitantly administered drug. An inducer of liver enzyme such as carbamazepine would expect to reduce plasma MT concentration whereas inhibitors such as cimetidine and fluvoxamine would expect to raise it. *In vitro*, MT was shown to have little enzymatic inhibitory effects whereas *in vivo* in rats, high doses (80mg/kg) of MT were shown to induce enzymatic activity. Confirmation in studies with humans is deemed necessary. Its only pharmacologically active metabolite, desmethylmirtazapine, contributes to only 3-10% of its pharmacodynamic activity.

Dosing

Initial dose, onset of efficacy, maintenance, duration

Usual starting dose is 30mg given once daily at bedtime with a dosage range of 15-45mg per day and titration of dose is usually not necessary. Food does not appear to affect the onset and extent of MT absorption. MT is

usually well tolerated in the elderly with drowsiness and dry mouth being the most common side effects. A lower daily dose may be necessary in the elderly.

In a pooled analysis, a responder rate of approximately 50% of the MT patients (compared to approximately 40% of the patients receiving fluoxetine, paroxetine or citalopram) was observed at week 3 of the treatment as measured by a reduction of at least 50% of the Ham-D scores.

Maintenance and duration of therapy is dependent on the severity and recurrence of depressive episode and is highly variable.

Plasma drug levels

Although no concentration-clinical response relationship could be established, therapeutic dosages of MT (15-45mg/day) result in plasma levels ranging between 5 and 100ug/L. It is interesting to note that plasma levels in females were found to be significantly higher than in males irrespective of age.

Combination /Augmentation Strategies

A recent double-blind study showed a significantly higher response rate to the combination of paroxetine and MT than monotherapy of either drug, and a 64% response rate to a switch to combination therapy for patients who have not responded to monotherapy. Other benefits of this combination may include reduced sexual dysfunction, weight gain and sedation. In another augmentation study, lithium was added to augment non-responders of imipramine and MT. Lithium augmentation was more efficacious in patients receiving imipramine however more patients had to be discontinued due to side effects.

Switching MT

From SSRI

There is a recent case report of a possible serotonin syndrome induced by MT (30mg/day) that was added to a 26-year-old white woman receiving fluvoxamine (200mg/day). Although it appears that concomitant administration poses no concern for serious drug interactions, a cross-taper is highly recommended.

From TCAs

From Nefazodone

From Venlafaxine

From Bupropion

A cross-taper is highly recommended when switching between these agents.

From Monoamine oxidase inhibitors (MAOI)

A washout period of at least 10 days is highly recommended. MT should not be combined with an MAOI.

Tolerability

Sleep/Sedation

MT seems to facilitate sleep without reducing daytime alertness. It improves the total sleep by enhancing sleep architecture such as increasing REM, Stage II, sleep efficiency and slow wave movement. Patients generally have easier and quicker time falling asleep and more restful quality of sleep. In contrast, both SSRIs and TCAs tend to reduce REM sleep. Sedation is dose-dependent and is one of the most common side effects.

Weight changes/Increased appetite

MT can induce weight gain early in the treatment perhaps by its stimulant effect on the appetite center of the brain and its anti-H₁ and anti-5HT_{2c} effects. A gain of 10-20 lb may result over a 6-week treatment period. In general, if a significant weight gain is not observed at the 6th week of treatment with MT, any significant weight gain will not likely occur at week 52.

Sexual functioning

There is one case report of sexual dysfunction associated with MT. While his depression improved within 3 weeks of MT treatment at a dose of 30mg daily, a 30-year-old white male reported that he was unable to ejaculate, despite full sexual interest and full erection. Within 5 days of discontinuation, he was able to achieve full orgasm just as before initiation of MT. Although MT, with its serotonin-2 receptor antagonism, appears to cause fewer sexual problems in both men and women and appears to be a useful antidepressant for patients who had experienced SSRI-induced sexual dysfunction, its propensity to cause sexual dysfunction should not be completely ruled out.

Overdose

Overall, MT appears to be safe in overdose. Most patients experienced only minor symptoms in doses up to about 30 times the maximum daily dose. A review of eight cases revealed only one patient with significant changes to electrocardiogram (ECG) and four with central nervous system (CNS) depressant effects. No seizures were reported. All patients recovered with no serious adverse effects.

Neutropenia

Post marketing surveillance revealed 16 cases of reversible agranulocytosis since its introduction in 1994. A complete blood count and liver enzyme measurement may be obtained if warranted.

Hormonal effects

MT seems to inhibit cortisol secretions in physically and mentally healthy young males (20-35 years old). The growth hormone and prolactin secretions appear unaffected by MT. The clinical relevance of this phenomenon is the fact that hypercortisolism is observed in depressed individuals and that normalization of cortisol secretion may contribute to the mechanism of action of the novel antidepressants.

Other effects

MT has few cardiovascular effects such as orthostatic hypotension. There is no evidence of hepatotoxicity to date. Dry mouth, constipation, dizziness, seizures, asthenia and elevated levels of cholesterol, triglyceride and alanine aminotransferase (ALT) can also occur.

Other Potential Use

Schizophrenia

MT (30mg Daily) as an add-on therapy to haloperidol (5mg daily) significantly reduced negative symptoms as determined by the Positive and Negative Syndrome Scale (PANSS) as well as the Clinical Global Impression (CGI) scores over a 6 week period in 30 patients diagnosed with DSM-IV criteria for schizophrenia. It is proposed that blockade 5-HT₂ of receptors may be key to reduction of negative symptoms as well as extrapyramidal side effects.

Autism

In an open-label study involving patients with autism and related pervasive developmental disorders, 7 out of 26 patients (aged 4-23 years) who were treated with MT (7.5-45mg/day) for at least 4 weeks showed “much improved to very much improved” improvements on the CGI Improvement scale.

Cost/Availability

MT is currently available in 30mg strength at a cost of \$1.30 per tablet.

Summary

MT has minimal cardiovascular and anticholinergic effects, safer overdose profile than TCAs and minimal effects commonly seen with SSRIs such as gastrointestinal symptoms, insomnia, restlessness and sexual dysfunction. However, sedation, weight gain and dry mouth may limit its use.

Conclusion

MT, a novel dual-acting antidepressant, enhances both noradrenergic and specific serotonergic neurotransmission but unlike venlafaxine, it is not a reuptake inhibitor. MT may be helpful in patients whose depression is characterized by anxiety, sleep disturbance, increased cortisol secretion, weight loss and gastrointestinal symptoms such as nausea and lack of appetite. It may also be helpful in those who may have had difficulty with sexual functioning, especially those who had been tried on SSRIs. Additional studies and clinical experience will provide more information about MT.

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