

CLINICAL VIGNETTE

Dose-Dependent Sedating and Stimulating Effects of Mirtazapine

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Case Report

A 90-year-old woman was hospitalized for failure to thrive, deconditioning, fatigue, and chronic intractable lower extremity pain from a leg wound. She complained of insomnia and received different sleeping pills on different days and was finally given a dose of mirtazapine 7.5 mg. She subsequently became somnolent and was barely arousable the next day. Workup for delirium was non-revealing. Mirtazapine was discontinued, and her sedation progressively resolved.

Discussion

Mirtazapine is a widely used antidepressant for major depressive disorder and has a unique pharmacologic profile. Its well-known ability to promote sleep, and occasionally cause weight gain, makes it a good option to address the insomnia, anorexia, and weight loss that often accompany depression in older adults.

Mirtazapine has multiple pharmacological actions that contribute to its effects on sleep. It produces its antidepressant effects primarily by antagonizing alpha 2 adrenergic receptors on both norepinephrine and serotonin (5-HT) presynaptic axons, while also antagonizing post-synaptic 5-HT subtype 2 and 3 receptors, which leads to increased release of norepinephrine and enhanced specific (5-HT₁ only) serotonin activity.¹ Although pre-synaptic activity on serotonin axons increases serotonin release, the antagonizing of type 2 and 3 post-synaptic serotonin receptors leads to selective enhancement of only the type 1 receptor activity. Unlike other antidepressants, mirtazapine does not employ serotonin or norepinephrine reuptake blockade as its main pharmacologic action.

Serotonin has a complex effect on sleep and its array of receptor subtypes are involved in different effects. 5-HT 2a and 5-HT 2c receptors play a role in reducing REM and slow wave sleep; thus, antagonism of these receptors promotes sleep.²⁻⁴ Mirtazapine at low doses also has a high affinity for the histamine-1 receptor.⁵ Both the histaminic and serotonergic effects contribute to increased sedation. However, the dose of mirtazapine is critical to its effects on sleep. At low doses, mirtazapine preferentially blocks the histamine receptor, since at lower plasma concentrations it has a higher affinity to histamine receptors than to serotonergic receptors. Consequently, there is increased duration of sleep at

low plasma concentrations and increased sedation at low doses of mirtazapine.⁶ At higher doses, the antihistamine activity is offset by increased noradrenergic transmission, which reduces its sedating effect.^{4,7} This was confirmed in a German study, which noted negative correlations between plasma mirtazapine concentration and both sedation and duration of sleep in the first week of treatment.⁸

In our case, 7.5 mg of daily mirtazapine was excessively sedating to our 90-year-old hospitalized patient. At the 15 mg dose, the norepinephrine effects of mirtazapine would have likely reduced the sedating effects of histamine and serotonin. In a comparison of clinical trials of mirtazapine in Europe versus the United States, less sedation was seen in the European studies that used higher initial doses of mirtazapine (15-20 mg) than in the US studies that used lower initial doses (5-10 mg).⁹ Therefore in order to reduce sedation, it has been suggested that mirtazapine be initiated at higher doses as high as 30 mg or more daily in younger patients.^{4,10,11}

It should be noted, however, that although sedation is an expected effect of the agent, it is usually most noticeable in the first few weeks of therapy and diminishes with continued treatment.¹² Tolerance to mirtazapine's histaminic effects develops 7-10 days after beginning treatment.⁴ This was confirmed in a placebo-controlled study with severe long-term sedation occurring in only 1 of 49 treated patients.¹³

A recent systematic review of studies of mirtazapine's sustained effects on sleep in major depressive disorder found mirtazapine to consistently improve sleep efficiency, total sleep time and sleep quality.⁴ In addition, specific improvements in sleep in patients treated with mirtazapine were better than those on other antidepressants.⁴

Mirtazapine effects on sleep quality include shortened time-to-onset of sleep, reduced stage I sleep, increased deep sleep, increased latency of REM sleep, reduced nighttime awakening,¹⁴ and improved sleep continuity while preserving sleep architecture.¹⁵ These sleep-promoting effects of mirtazapine have to be balanced against its risk for excessive sedation; the latter is more pronounced at lower doses and in the first weeks of therapy.

In contrast to the risk of excessive sedation at low doses, mirtazapine at higher doses can be over-stimulating in older adults as norepinephrine effects overwhelm the sedating effects of serotonin. Thus, for instance, mirtazapine at 45 mg daily can cause insomnia when given at bedtime. Peak plasma concentrations are achieved 90 minutes after an oral dose, and half-life is around 16 hours.⁷ Thus, morning administration of higher doses of mirtazapine means lower plasma norepinephrine concentrations at night than bedtime dosing, which is less likely to interfere with sleep.

Conclusion

Mirtazapine is a noradrenergic and specific serotonergic antidepressant and has an unusual dose-dependent effect on sleep. At low doses below those needed for antidepressant efficacy, mirtazapine binds more avidly to the histamine site than to the adrenergic sites, leading to increased daytime sedation. Sedation is inversely related to dose and may be excessive in older adults on the 7.5 mg daily dose. For this drug, the usual adage for pharmacotherapy in older adults: 'Start low, titrate up slow' needs to be reconsidered. We should avoid 7.5 mg dosing of mirtazapine in older adults and start at 15 mg instead. The medication is not as overly sedating at 15 mg because the norepinephrine effects moderate the sedating effects of serotonin, while still maintaining its soporific properties. However, at higher doses, the norepinephrine effects may also interfere with sleep. In such cases, switching the administration from bedtime to the morning can correct a patient's insomnia.

Contrary to the general principle that lower doses tend to have less side effects, the opposite is the case for mirtazapine and excessive sedation. This should prompt us to re-evaluate the initial dosing of mirtazapine in older patients and remain vigilant with dose-titration and monitoring for adverse reactions.

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