

Low-Dose Mirtazapine-Induced Nightmares Necessitating its Discontinuation in a Young Adult Female

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Abstract

Mirtazapine is a novel tetracyclic antidepressant which enhances noradrenergic and serotonergic transmission by blocking central α_2 -adrenergic auto- and hetero-receptors. Due to favorable safety and adverse effect profile, it is often viewed as a promising agent for treatment of depression. Particularly, its anxiolytic and sleep-improving properties have led to its favorable positioning for the management of depression with insomnia. Our objective is to describe a case of depression with treatment-emergent nightmares induced by mirtazapine. A 21-year-old female medical student was diagnosed with moderate depression with prominent insomnia and initiated on tablet mirtazapine 7.5 mg subsequent to a failed trial of selective serotonin reuptake inhibitor. On each of the next 7 days, she developed nightmares that were quite distressing and terrifying. As per the patient's request, tablets were stopped. The side effect abated within 2 days of stopping the agent, and this close temporal relationship suggests a causal role for mirtazapine in inducing the adverse reaction. Nightmares are usually associated with rapid eye movement (REM) sleep, and literature is inconsistent about the effect of mirtazapine on REM sleep parameters. Nevertheless, clinicians need to be forewarned about the possibility of developing treatment-limiting REM sleep phenomena such as nightmares when using antidepressants without prominent REM suppressant properties such as mirtazapine. The putative mechanisms behind these rare adverse reactions are discussed.

Keywords: Adverse drug reaction, mirtazapine, nightmares, pharmacovigilance, rapid eye movement sleep, parasomnias

INTRODUCTION

Mirtazapine is a relatively new and novel dual-acting tetracyclic antidepressant belonging to the piperazine group. It increases noradrenergic and serotonergic transmission mainly through blockade of central α_2 -adrenergic auto- and hetero-receptors. The increased release of serotonin is mainly channelized toward stimulation of 5HT-1 receptor as the drug directly blocks 5HT-2 and 5HT-3 receptors. This dual enhancement of noradrenergic and 5HT-1 receptor activity is thought to underlie the antidepressant properties of mirtazapine.^[1] Preliminary comparisons of mirtazapine against selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitor venlafaxine suggest comparable efficacy but a significantly faster onset of action for mirtazapine with beneficial effects often seen as early as 1–2 weeks after treatment initiation.^[2] A large well-conducted meta-analysis of randomized controlled trials has concluded that mirtazapine has superior efficacy when compared to 12 other antidepressants.^[3] These findings, coupled with favorable short-term tolerability data, make many

clinicians favor mirtazapine for pharmacological treatment of depression. Initially, the high incidence of somnolence noted in trials with mirtazapine led to leveraging of this side effect for the management of insomnia. In a double-blind placebo-controlled trial on healthy volunteers given a single dose of 30 mg mirtazapine, the authors noted increased sleep continuity and efficiency in the mirtazapine arm. Further, prolongation of slow-wave sleep was also observed.^[4] A study that directly compared mirtazapine versus fluoxetine, an SSRI, for the treatment of depressed patients with insomnia demonstrated significant advantages for mirtazapine in terms of improving total sleep time and sleep latency.^[5]

While the sleep-inducing properties of mirtazapine are thought to be mediated through blockade of central

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histaminergic receptors (H1), the prolongation of slow-wave sleep is attributed to 5-HT_{2A/C} antagonism.^[6] Interestingly, tolerance may develop to the sleep-inducing properties of the drug-mediated through H1 antagonism. This was supported by Radhakishun *et al.*^[7] in a two-arm parallel comparison of two dosages (15 mg vs. 30 mg) of mirtazapine wherein the authors noted that the initial 10% incidence of insomnia gradually decreased as the study progressed which suggested development of tolerance to the adverse reaction. Subsequently, evidence from other clinical studies have also indicated that mirtazapine-induced sedation diminishes over time.^[8] Nevertheless, owing to these sedating properties, mirtazapine is often preferred for depressed clients with prominent insomnia. Of note, these sedating effects are often accompanied by lack of rapid eye movement (REM) suppression that is seen with most other conventional antidepressants. We describe the case of a young adult female who developed distressing nightmares with mirtazapine necessitating its discontinuation.

CASE REPORT

A 21-year-old female medical student presented with a history of tearfulness, loss of interest and drive in performing her hobbies and personal routines, lethargy together with ideas of self-harm, marked insomnia, and loss of appetite following a relationship breakup. Of these symptoms, the insomnia was particularly “crippling,” and as a result, she could not attend her classes or focus on her rotations. We made a diagnosis of moderate depression. Following nonresponse to a trial of tablet escitalopram 20 mg for 8 weeks, we tapered this medication (over a period of 6 weeks) and initiated her on tablet mirtazapine 7.5 mg to leverage its sedating potential. Four days after starting mirtazapine, she reported terrifying dreams that would make her shout and scream in her sleep every night. Her mother also noticed these disturbances and was quite alarmed. We reassured them and continued treatment with the same dose. Over the next 3 days, these nightmares recurred daily and her sleep was fitful and nonrestorative. Consequent to these distressing side effects and patient’s request to change medications, we decided to stop tablet mirtazapine and started tablet sertraline 50 mg along with supportive psychotherapy to manage her relationship stressor. The nightmares abated within 2 days of stopping mirtazapine. There were no other concurrent medications.

DISCUSSION

The temporal relationship between initiation of mirtazapine and appearance of nightmares and its subsequent disappearance consequent to stoppage of the drug suggests a causal relationship in the present case. As per the Naranjo adverse drug reaction scale,^[9] the association is classified as probable. A possibility of SSRI discontinuation syndrome was also considered, but two factors pointed against this possibility: first, the escitalopram had been tapered gradually, and second, the isolated presence of one symptom (nightmares) which is inadequate for a diagnosis of SSRI discontinuation syndrome.^[10]

Only two cases of mirtazapine-induced nightmares have been reported previously.^[11,12] Both of them described patients who developed the side effect with 15 mg mirtazapine and had a prior history of similar reactions to the same agent. To the best of our knowledge, this is the first report of nightmares with a lower dose of mirtazapine and with no incriminating history. Most traditional antidepressants have REM suppressant properties with some research supporting the notion that the antidepressant property itself is linked to REM sleep deprivation.^[13] When administered acutely, mirtazapine has been shown to promote REM sleep together with shortening of sleep onset, increased total sleep time, and slow-wave sleep.^[14] This may explain the nightmares in some patients.

On a discordant note, investigators who studied the effects of single dose of 30 mg mirtazapine on the sleep polysomnogram for the next 3 days failed to show any significant effect on REM sleep variables.^[8] Moreover, they demonstrated a significant increase in slow-wave sleep and suggested that the neurochemical basis for this effect may be linked to its 5-HT₂-receptor antagonism. Given that this property of 5-HT₂ blockade is also shared by many other compounds such as nefazodone, trimipramine, bupropion, and moclobemide, it may be worth investigating its benefit in depressed populations.^[15] Apart from these two agents, other antidepressants without documented REM suppressant action include though rarely seen, all the three reported cases of mirtazapine-induced nightmares, including the present one, required discontinuation of the offending agent. Hence, future research should delineate patient characteristics that may predispose to such adverse drug reactions so as to guide the choice of antidepressant, in the process, saving valuable time and resources. Given the conflicting state of evidence on effect of mirtazapine on REM sleep, more large-scale, well-designed trials are also required to improve our understanding of the effects of this compound on sleep variables and how this may be linked to its antidepressant action.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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