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Restless Leg Syndrome and Its Relation to Mirtazapine: A Case Report

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Abstract

Major depressive disorder (MDD) and Restless legs syndrome (RLS) present complex clinical challenges, often coexisting and complicating treatment strategies. While the relationship between MDD and RLS remains somewhat elusive, emerging evidence suggests a potential interplay between antidepressant medications and the worsening of RLS symptoms. This case report illuminates an instance where mirtazapine, a tetracyclic antidepressant commonly used in MDD, precipitated a resurgence of RLS symptoms in a patient with a previously controlled presentation.

Keywords

case report, mirtazapine, restless leg syndrome, RLS, gerontology, depression

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Introduction

Major depressive disorder (MDD) is a common mental health condition characterized by various symptoms, including cognitive impairment, disrupted sleep health, and anhedonia for at least 2 weeks consistently (National Institute of Mental Health, 2023; Otte et al., 2016). Pharmacotherapy for MDD typically involves the use of selective serotonin reuptake inhibitors (SSRIs) as first-line agents, with alternative antidepressants such as mirtazapine reserved for treatment-resistant cases (Ruberto et al., 2020). Despite its efficacy, mirtazapine is associated with a spectrum of adverse effects, including sedation, weight gain, and the onset or exacerbation of Restless legs syndrome (RLS) (Jilani et al., 2022). RLS is a neurological disorder described as an irresistible urge to move the legs, especially at night. RLS is difficult to treat due to its multifactorial nature, but treatment options often involve the use of dopamine agonists or other pharmacological interventions (Gossard et al., 2021).

Case Report

An 81-year-old female with a history of MDD, generalized anxiety disorder, hypertension, and RLS presented to the clinic with recurrent depressive symptoms. She was referred to our clinic for treatment and management of her MDD. The patient had been diagnosed with MDD several years prior, and her mood and responses during the clinic visit were consistent with this diagnosis. A mental status examination was conducted to assess her baseline mental function, which supported the diagnosis of MDD without psychotic features. She has tried various antidepressants, including bupropion, fluoxetine, duloxetine, and escitalopram, yet her depression and anxiety symptoms persisted. Notably, the patient had effectively managed her RLS with pramipexole until the initiation of mirtazapine. Our patient was on a drug regimen that effectively controlled her blood pressure; before her mirtazapine prescription, her blood pressure was 112 systolic in the clinic. She was taking 0.5 mg of pramipexole orally three times daily and was started on a low trial dose of 7.5 mg of mirtazapine nightly. If the patient tolerated the mirtazapine well, the dosage was to be gradually increased during subsequent clinic visits. However, after 2 weeks of mirtazapine use, the patient reported systolic blood pressure fluctuating between 112 and 196 mmHg within a single day. Subsequently, at the follow-up visit, about 4 weeks after she was initially prescribed mirtazapine, the antidepressant was discontinued and substituted with vortioxetine, an SSRI. Following this change, the patient reported that her RLS symptoms had improved

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and were once again well controlled with her previous medication, pramipexole, a dopamine agonist. The dramatic exacerbation and subsequent improvement of the patient's RLS symptoms following mirtazapine initiation and withdrawal, respectively, highlight the potential factors that physicians should consider when prescribing antidepressants in patients managing comorbid psychiatric and neurological conditions.

Discussion

The co-occurrence of MDD and RLS presents intricate therapeutic challenges, particularly regarding the selection of antidepressant agents. While mirtazapine demonstrates efficacy in managing depressive symptoms, its potential to induce or exacerbate RLS emphasizes the necessity of careful medication selection. There is extensive documentation of the relationship between mirtazapine use and movement disorders, particularly RLS. Mechanistically, the interaction between mirtazapine and RLS remains incompletely understood, although disruptions in the dopaminergic and opioid pathways have been implicated (Brown et al., 2005; Kolla et al., 2018; Rissardo & Caprara, 2020). One proposed theory of antidepressant-induced RLS suggests the overstimulation of the central nervous system. According to this theory, increasing the concentration of serotonin and norepinephrine, while also increasing the concentration of dopaminergic pathways may predispose patients to movement disorders and RLS-like symptoms (Patatanian & Claborn, 2018). According to a literature review conducted by Rissardo and Caprara (2020) mirtazapine is associated with multiple movement-related disorders including RLS, tremors, akathisia, dystonia, periodic limb movement disorders, dyskinesia, parkinsonism-like symptoms, and rapid eye movement behavior disorders. One proposed theory by Rissardo and Caprara (2020) suggests antagonistic interactions of 5HT2A and 5HT2C serotoninergic receptors may induce the release of norepinephrine by postganglionic adrenal glands, therefore increasing the concentration of serotonin in the brainstem and exacerbating RLS symptoms. Additionally, another pathway may be involved that simultaneously increases the firing rate of the raphe nuclei, leading to further release of norepinephrine from the adrenal glands. Additionally, a literature review conducted by Kolla et al. (2018) identified that although many patients were identified as having RLS symptoms after being prescribed mirtazapine, only the older patients mentioned these side effects to their provider. These findings may suggest that (a) although mirtazapine may cause RLS symptoms, the symptoms are not severe enough to be of clinical significance to some patients and (b) age may play a factor in the manifestation of mirtazapine-induced RLS symptoms (Kolla et al., 2018). Interestingly, discontinuing mirtazapine has been shown to reduce or completely eliminate RLS symptoms in affected patients (Rissardo & Caprara, 2020).

After reviewing the literature, several risk factors have been identified that increase the likelihood of developing restless legs syndrome (RLS) or experiencing a worsening of symptoms following the initiation of mirtazapine treatment. These risk factors include age, comorbidities, and the use of antipsychotics, dopamine antagonists, and tricyclic antidepressants (Kim et al., 2008; Patatanian & Claborn, 2018). Our patient was an elderly woman with comorbidities, but she was not prescribed antipsychotics, tricyclic antidepressants, or dopamine agonists to manage her symptoms. Interestingly, she was on a dopamine agonist when she saw an exacerbation of her RLS symptoms after adding mirtazapine to her drug regimen. This case, along with the current body of literature, highlights a potential avenue for research and exploration. Future research efforts should focus on elucidating mirtazapine's drug interactions, its effect on the dopaminergic pathway factors, and its ability to precipitate movement disorders, particularly RLS, in older patients.

The high prevalence of depression and depression-like symptoms in patients with RLS underscores the need to explore the interaction between antidepressants, including mirtazapine, and their mechanisms of action to elucidate the relationship between mirtazapine and RLS (Rottach et al., 2008). A retrospective chart review conducted by Kim et al. (2008) attempted to identify the factors that increased the risk of depressed patients developing RLS. The study concluded that dopamine antagonists and the use of tramadol may potentiate the risk of depressed patients developing RLS. In our case report, however, our patient was originally on a dopamine agonist while taking her initial, low dose of mirtazapine. This discrepancy highlights the complex interactions between mirtazapine and RLS symptoms and provides an opportunity for further investigation (Kim et al., 2008). Moreover, there is a need for more evidence-based protocols for older adults with complex depression. Alternative treatment options must be considered for this complex patient population, especially for those who have neurological comorbidities. For example, neuromodulatory therapies such as electroconvulsive therapy has been shown to be effective in treating treatment-resistant depression, and it may be a viable alternative for patients who can tolerate treatment (Pope et al., 2022). Transcranial magnetic stimulation (TMS) is another effective neuromodulatory therapy used by providers for treatment-resistant depression (Somani & Kar, 2019). This therapy is designed to alleviate the asymmetry in frontal lobe functionality observed in patients with depression. TMS utilizes repetitive low-frequency ($\leq$1 Hz) stimulation to inhibit the right dorsolateral prefrontal cortex or high-frequency ($\geq$1 Hz) stimulation to activate the left dorsolateral prefrontal cortex. Both high- and low-frequency TMS have demonstrated efficacy in managing major depressive disorder (MDD) in treatment-resistant patients (Somani & Kar, 2019). Although this modality is relatively new, it is

gaining traction as a viable treatment option for elderly patients with treatment-resistant depression who may be unable to tolerate conventional drug therapies or electroconvulsive therapy (ECT) due to their adverse effects (Somani & Kar, 2019).

Conclusion

Clinicians should exercise caution when prescribing mirtazapine to patients with preexisting RLS, especially in elderly patients who often have comorbidities, as the drug can precipitate symptom resurgence despite prior adequate control. This case adds to the growing body of literature on mirtazapine's adverse effects in patients with movement disorder comorbidities, emphasizing the importance of personalized treatment approaches in managing complex, elderly psychiatric cases while considering both the potential benefits and adverse effects of pharmacotherapy.

Declaration of Conflicting Interests

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Ethical Considerations

Our institution does not require ethical approval for reporting individual cases or case series.

Consent to Participate and Consent for Publication

The patient provided consent for their deidentified medical information to be published in a medical journal.

Data Availability

All data underlying the results are available as part of the article and no additional source data are required.

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