

Balancing Sleep and Motor Symptoms: A Case Report of Managing Insomnia in Parkinson's Disease

Meghan Ha¹, Nishita S. Amin¹, Katie Meyers², Jacques Turgeon^{3,4} and Chandni Bardolia^{1*}

¹Tabula Rasa HealthCare, Applied Precision Pharmacotherapy Institute, USA

²Tabula Rasa HealthCare, Learning and Development, USA

³Tabula Rasa HealthCare, Precision Pharmacotherapy Research and Development Institute, USA

⁴Faculty of Pharmacy, University de Montréal, Canada

Abstract

Objective: The management of insomnia presents as a challenge for many Parkinson's disease patients and their care teams. Insomnia in patients with Parkinson's disease may be attributed to the side effect profile of several medications that are commonly used to treat Parkinson's disease. Additionally, the progression of the disease is associated with disruption of circadian rhythms, nocturnal symptoms, blunted melatonin secretion, and late melatonin onset. This case report aims to demonstrate how a patient's Parkinson's medication profile could be optimized to control motor symptoms and reduce the occurrence of insomnia through the use of comprehensive medication review services.

Case report: A 71-year-old male with Parkinson's disease was developing severe symptoms of tardive dyskinesia due to his chronic carbidopa/levodopa/entacapone therapy. In order to address the tardive dyskinesia, entacapone was discontinued and amantadine was initiated to offset the stiffness and bradykinesia. The addition of amantadine resulted in nightmares and poor sleep quality, even though the patient was already taking mirtazapine to treat his depressive status and insomnia. The patient's healthcare team collaborated with a clinical pharmacist to adjust the Parkinson's disease regimen and mirtazapine dosage, all of which resulted in notable improvements in his reported insomnia and quality of life.

Discussion and Conclusion: Optimizing motor control in patients with Parkinson's disease, while mitigating insomnia side effects of medications can be a very complex process. The main goal for patients who encounter this problem is to enhance their Parkinson's disease therapy by identifying medications that can contribute to insomnia while addressing the patient's symptoms and disease progression. Alternative treatments to manage insomnia in patients with Parkinson's disease should also be considered, including the addition of melatonin and/or the use of bright light therapy.

Keywords: Insomnia • Bradykinesia • Parkinson's disease • Tardive dyskinesia • Mirtazapine • Amantadine • Entacapone • Motor symptoms • Sleep • Melatonin • Bright light therapy • Comprehensive medication reviews

Abbreviations: PD: Parkinson's Disease; L-Dopa: Levodopa; COMT: Catechol-O-Methyltransferase; SNF: Skilled Nursing Facility; TD: Tardive Dyskinesia; MDD: Major Depressive Disorder; BLT: Bright Light Therapy

Introduction

Parkinson's Disease (PD) is commonly referred to as a disorder of the extrapyramidal system [1]. Its diagnosis requires the presence of bradykinesia and at least one of the following hallmark motor features: muscular rigidity, resting tremor, and/or postural instability [2]. Although the pathogenesis of PD is not explicitly known, evidence suggests an association between the degeneration of dopaminergic neurons in the substantia nigra region of the brain and the severity of cardinal motor features [3,4]. Dopamine is a neurotransmitter that is critical for muscle coordination and movement; therefore, a reduction in dopamine results in motor impediment [4].

Levodopa (L-dopa) is a precursor to dopamine and functions as dopamine replacement in patients with motor disorders [5]. Carbidopa is a medication that prevents peripheral metabolism of L-dopa by directly inhibiting the dopa

decarboxylase enzymes, therefore providing additional treatment efficacy when used in conjunction with L-dopa [5]. The carbidopa/levodopa combination is considered the standard of PD therapy [5]. Unfortunately, long-term L-dopa therapy can result in a variety of motor complications, including dose "wearing-off" and peak-dose dyskinesias [6]. With each year of L-dopa therapy, a patient's risk of developing motor fluctuations or dyskinesia increases by 10% [3,7].

The Catechol-O-Methyltransferase (COMT) inhibitor, entacapone, can be a useful add-on therapy to help attenuate motor fluctuations in carbidopa/levodopa-treated patients [8]. On the other hand, entacapone can contribute to the early development of dyskinesias (25% occurrence rate) [9]. Amantadine is an agent used in PD to treat dyskinesias associated with peak-dose carbidopa/levodopa and is commonly added to a medication regimen in moderate to severe stages of PD. It is associated with various anticholinergic side effects, such as orthostatic hypotension ($\leq 29\%$), dizziness ($\leq 29\%$) and insomnia (5-10%) [10].

The inability to initiate or maintain sleep is a frequent symptom in patients with PD [11]. Insomnia is likely to occur as the disease progresses, as sleep is often disrupted by the increasing nocturnal symptoms of rigidity, motor fluctuations, and pain [12]. Medications such as selegiline, amantadine and other drugs with anticholinergic properties can contribute to insomnia in patients with PD [13].

The disruption of circadian rhythms has also been observed in patients with PD [13]. Accompanying this is a blunting of melatonin secretion which

*Address for Correspondence: Bardolia C, Drug Information Specialist, Tabula Rasa HealthCare, Applied Precision Pharmacotherapy Institute, USA, E-mail: cbardolia@trhc.com

Copyright: © 2021 Ha M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Received 10 March 2021; **Accepted** 24 March 2021; **Published** 31 March 2021

correlates with symptoms of excessive daytime sleepiness [14]. According to Bolitho et al., patients with PD treated with dopaminergic medications were found to have a phase-advanced melatonin onset (i.e., an earlier shift in circadian rhythm) relative to sleep onset, reinforcing the postulation that dopamine therapy may play a role in circadian disruption [8,13]. The purpose of this case report is to highlight these concepts and identify how to optimize the medication profile of a patient with PD to control motor symptoms and reduce the occurrence of insomnia through the use of comprehensive medication review services.

Case Report

The following information for this patient case report was collected through discussions with the patient's healthcare team and use of electronic health records. Seeking assistance in treating uncontrolled PD symptoms, the provider consulted a clinical pharmacist about medication management for an older patient.

A 71-year-old male with a past medical history of benign prostatic hyperplasia, hyperlipidemia, PD, type 2 diabetes, hypertension, atrial fibrillation, generalized anxiety disorder, major depressive disorder (MDD), and dementia was admitted to a skilled nursing facility (SNF) after a fall at his nursing home. SNF admission occurred for the management of the patient's severe tardive dyskinesia (TD) that resulted from chronic treatment with carbidopa/levodopa/entacapone. As a first step, the patient's entacapone therapy was discontinued to counter the severity of his TD symptoms period. Unfortunately, the removal

of entacapone worsened his immobility. Amantadine 100 mg was then initiated once daily in the morning to address the stiffness and bradykinesia that he was experiencing. The patient was also taking ropinirole 2 mg for PD and mirtazapine 15 mg for mood and sleep management and weight gain. A full list of the patient's medications that was reviewed upon SNF admission can be found in Table 1, and a detailed timeline following the patient's case can be observed in Figure 1.

After the addition of amantadine, the patient continued to experience TD symptoms; however, they were not as burdensome as they were before entacapone was discontinued. He began having severe nightmares the day after his first amantadine dose and routinely slept for only 2 hours every night for the next two weeks. At this point in time, the provider consulted the clinical pharmacist who recommended decreasing the dose of mirtazapine from 15 mg to 7.5 mg to address the patient's issues with sleep in addition to his MDD.

Almost one week later, the patient experienced a second fall. He sustained no injuries from the fall, but his SNF stay was extended as a result. The dose of amantadine was reduced from 100 mg to 50 mg once daily for better management of dyskinesias and to reduce the risk of orthostasis. Following the fall incident, the patient had a resting blood pressure of 159/94 mmHg, for which his healthcare provider initiated amlodipine 10 mg once daily. Staff members who followed up three days after the fall incident and medication adjustments reported that the patient's sleep quality significantly improved and that he was experiencing less dyskinesia.

Five days following the status improvement (four weeks after the addition of amantadine), the patient began exhibiting severe bradykinesia and required

Table 1. Comprehensive List of Medications; This table provides an overview of the patient's medication list and medication changes made.

Medications	Medication Changes
Cholecalciferol 1000-unit tablet once daily	Unchanged
Ketoconazole 20 mg/mL medicated shampoo as directed	Unchanged
Ropinirole 2 mg ER tablet once daily	Unchanged
Ketoconazole 20 mg/mL topical cream as needed	Unchanged
Polyethylene glycol 3350 17000 mg powder as needed	Unchanged
Amantadine 50 mg/5 mL oral solution 100 mg once daily in the morning	Originally at 100 mg, then decreased to 50 mg, then increased to 75 mg
Amlodipine 10 mg tablet once daily	New therapy initiation
Carbidopa/Levodopa 50-200 mg ER tablet once daily	Unchanged
Entacapone 200 mg tablet once daily	Discontinued
Mirtazapine 15 mg tablet once daily at bedtime	Originally at 15 mg, decreased dose to 7.5 mg

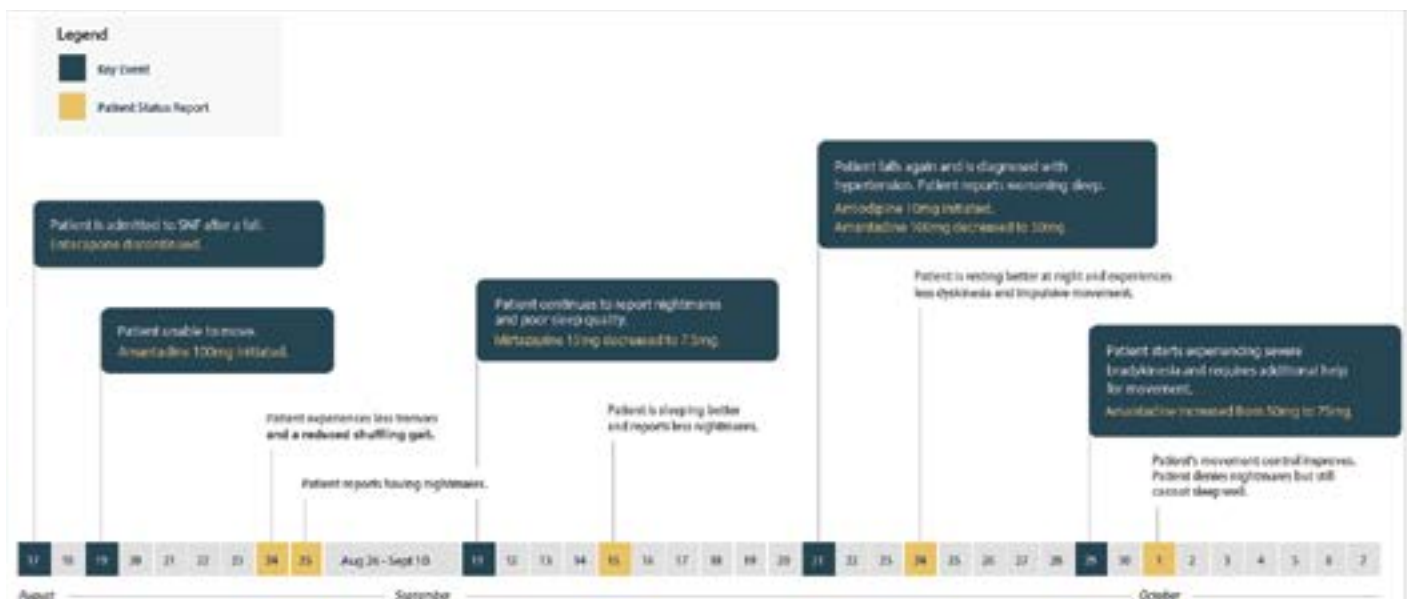


Figure 1. Patient case timeline: This figure visualizes the order of the events detailing this patient case, including key events that led to medication changes and the patient's status report following the medication changes.

increased assistance for mobility. Subsequently, the clinical pharmacist determined that the 50 mg dose of amantadine lacked the therapeutic efficacy to treat the patient's bradykinesia and suggested increasing the dose to 75 mg while being mindful of potential insomnia side effects. Following the dose increase, the patient regained his motor functionality, but his insomnia symptoms returned, although to a lesser degree than before.

In summary, the patient's healthcare team, in collaboration with a clinical pharmacist, adjusted the patient's PD medications in consideration of side effects and the newly initiated antihypertensive therapy, all of which may have contributed to better management of insomnia. The patient and provider determined that additional non-pharmacological therapies may be clinically warranted, and plans are being made to trial those options. The healthcare team decided to continue to monitor medication response to evaluate pharmacotherapy risks versus benefits as the patient progresses.

Discussion

The main goal for this patient was to optimize his current PD regimen and improve his quality of life by addressing his ongoing motor symptoms and reducing medication side effects. In this particular patient case, entacapone was causing TD while amantadine and mirtazapine were contributing to insomnia.

Amantadine at high doses (300 mg if used as monotherapy or 200 mg if used alongside other antiparkinson drugs) is stimulating due to its ability to enhance dopamine release [10,15]. As mentioned before, amantadine is used to manage tremor, rigidity, bradykinesia, and, most commonly, L-dopa-induced dyskinesia. Although its mechanism of action is not entirely clear, the drug is known to enhance dopamine release from pre-synaptic terminals and inhibit NMDA receptors [12]. Common side effects of amantadine include syncope ($\leq 29\%$), psychosis ($<25\%$), dizziness ($\leq 29\%$), orthostatic hypotension ($\leq 29\%$), insomnia (5-10%), abnormal dreams (1-5%), and dry mouth (1-16%) [10]. Elderly patients are particularly prone to developing confusion with amantadine use, but dividing amantadine into two daily doses of the IR formulation can help reduce CNS effects [10].

In this case, amantadine was added to treat the patient's L-dopa-induced dyskinesia; however, at the same time, it contributed to the worsening of his sleep quality. Orthostatic hypotension related to amantadine therapy could have contributed to the patient's second fall at the SNF. Based on these clinical observations, an initial dose reduction from 100 mg to 50 mg was proposed.

This lower dose of amantadine might have lessened the patient's risk of insomnia and orthostatic hypotension; however, 50 mg is considered to be sub-therapeutic for the treatment of motor symptoms [10]. Decreasing the dose of amantadine resulted in a return of the patient's bradykinesia. To optimize the therapeutic efficacy of amantadine while trying to balance the risk of side effects, the clinical pharmacist recommended a modest dose increase from 50 mg to 75 mg. Although current literature only supports the use of amantadine 100 mg to treat peak-dose levodopa, amantadine 75 mg proved to be a minimum effective dose for this patient through trial and error, with a clinically-guided approach.

Amantadine is primarily excreted unchanged (80-90%) in the urine and avoids metabolism through the liver [10]. Phase III studies found that healthy older males (≥ 60 years) have a significantly increased average half-life elimination of 29 hours compared to 16 hours in patients with normal renal

function [16]. This patient may experience diminished clearance of amantadine because of his low body weight and his age, so dose modifications should be prioritized. Careful titration strategies should be utilized in older patients to obtain clinical benefits while mitigating risks due to increased sensitivity to medication effects. In this particular patient case, the patient's bradykinesia improved with the dose increase from 50 mg to 75 mg.

The rationale for decreasing the mirtazapine dose from 15 mg to 7.5 mg was to promote sleep. Mirtazapine is an antidepressant that acts as a stimulant at high doses and as a histamine receptor antagonist at low doses [17]. It enhances noradrenergic and serotonergic activity by antagonizing adrenergic autoreceptors and serotonergic receptors [4]. Mirtazapine has a preferentially high affinity for histamine-1 receptors at low doses, which results in a histaminic and serotonergic blockade that contributes to sedation [9]. Higher doses are expected to provide a more noradrenergic effect and, thus, a higher degree of activation, leading to benefits in maintaining wakefulness [17,18]. The patient in this case benefited from the decreased dose of mirtazapine at bedtime because of its sleep-promoting sedative properties.

Another factor possibly contributing to the patient's sleeping problems was his uncontrolled hypertension. The patient's blood pressure reading of 159/94 mmHg indicated that he was hypertensive and not at goal per the American College of Cardiology and American Heart Association Guidelines [19]. The patient's medication list (Table 1) did not include antihypertensive medications prior to SNF admission. Hypertension can cause complications that contribute to difficulty in sleeping, and on the converse, chronic insomnia can also contribute to a higher risk of hypertension [20]. The patient was started on amlodipine 10 mg for better blood pressure control and sleep quality management. It is important to note that elderly and frail patients are more sensitive to blood pressure changes, especially when taking antihypertensive therapy, and they should be counseled to get up slowly to avoid syncope due to orthostatic hypotension.

Although improvements have been made to manage this patient's insomnia, additional low-risk therapies for sleep maintenance should be discussed. Melatonin is a hypnotic agent that can exert positive benefits for sleep in patients with PD who are experiencing insomnia, as its mechanism of action is to regulate the sleep-wake cycle [21]. Circadian rhythm disruptions in patients with PD can be addressed with melatonin's chronobiotic properties. Doses exceeding 5 mg rarely show greater benefit, but when used as a chronobiotic (i.e., an agent that can cause phase adjustment of circadian rhythms), melatonin doses can be significantly lower (0.5 mg or less) to avoid sedation, especially if given during the daytime [13].

Another low-risk alternative for sleep aid is a nonpharmacological treatment known as bright light therapy (BLT). BLT works by stimulating cells in the retina that connect to the hypothalamus, which helps control circadian rhythms [22]. Morning use of BLT has been found to be effective in treating sleep problems associated with circadian outcomes and insomnia symptoms. A caveat is that the effects of BLT are only maintained with ongoing therapy [13].

Due to the complexity of this patient's comorbidities, the medication changes required close monitoring for patient response and side effects. Such monitoring would not have been possible without the collaboration of the entire healthcare team. A general approach to balancing medication side effects with therapeutic efficacy is to adjust one medication at a time and assess the patient's response. The overall pharmacotherapy recommendations specific to this case report are summarized in Table 2.

Table 2. Overall Recommendation Summary; This table lists the recommendations made by the pharmacist in addressing insomnia and medication side effects in Parkinson's Disease for this patient case.

	Recommendations
	Reduce mirtazapine from 15mg to 7.5mg once daily.
Start amantadine at the lowest dose of 50mg and titrate up. Administer in the morning to avoid insomnia and consider using 2 divided daily doses of the IR formulation to minimize CNS effects.	
	Maintain blood pressure goals for better sleep quality.
	Consider bright light therapy, good sleep hygiene, and melatonin as safe and additional alternatives to address issues with sleep.

Conclusion

In conclusion, controlling motor symptoms in PD while mitigating side effects of insomnia is a medication balancing act. Due to the variability of side effects of PD medications, doses should be fine-tuned to the patient's symptoms, and only one medication should be adjusted at a time. For the patient discussed in this case report, although his insomnia symptoms weren't entirely alleviated, there was an observed improvement in the severity of his insomnia after medication adjustments were made. These dose changes should be continued throughout the course of his therapy as necessary to address the most pertinent side effect concern at the time, as it may not be possible to completely avoid all medication adverse events. Alternative solutions, including BLT and melatonin, are also being considered as add-on therapies for the treatment of insomnia in this patient with PD.

Acknowledgement

The authors would like to acknowledge Dana Filippoli, MBE, MPH for her support in the publication of this case report.

References

- Ashok E. Philip, George DeMaagd and Faruk Khan. "Parkinson's Disease and Its Management: Part 1: Disease Entity, Risk Factors, Pathophysiology, Clinical Presentation, and Diagnosis." *Med Chem Drug Affect Nervous Sys* 40 (2015): 504-532.
- Jankovic, Jose. "Parkinson's disease: clinical features and diagnosis." *J Neurol Neurosurg Psychiatr* 79 (2008): 368-376.
- Rajesh Pahwa and Kelly E. Lyons. "Options in the Treatment of Motor Fluctuations and Dyskinesias in Parkinson's Disease: A Brief Review." *Neurologic Clin* 3 (2004): 35-52.
- Jellinger, Kurt. "The Patho Mechanisms Underlying Parkinson's Disease." *Expert Rev Neurother* 2 (2014): 199-215.
- Susan H. Fox, Regina Katzenschlager, Shen-Yang Lim and Bernard Ravina, et al. "The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the Motor Symptoms of Parkinson's Disease." *Movement Disord* 26 (2011): 2-41.
- Khan, Tarannum. "Off Spells and Dyskinesias: Pharmacologic Management of Motor Complications." *Cleve Clin J Med* 79 (2012): 8-13.
- Thanvi Brooks and Lo Thanvi. "Long Term Motor Complications of Levodopa: Clinical Features, Mechanisms, and Management Strategies." *Postgrad Med J* 80 (2004): 452-458.
- Samuel Bolitho, Sharon Naismith, Shanthakumar Rajaratnam and Ron Grunstein, et al. "Disturbances in Melatonin Secretion and Circadian Sleep-Wake Regulation in Parkinson Disease." *Sleep Med* 15 (2014): 342-347.
- Shizuka Yamazaki and Yusuke Tanigawara. "Micromedex Healthcare Series." *Igaku Toshokan* 51 (2004): 239-242.
- Oscar Henry Mayer, John Karafilidis, Kate Higgins and Brian Griffin, et al. "Descriptive Characteristics of Males with Duchenne Muscular Dystrophy in Those Covered by Government (Medicaid) and Non-government (Private) Health Plans." *US Neurol* 14 (2018): 2-88.
- Klaus Seppi, Daniel Weintraub, Miguel Coelho and Santiago Perez-Lloret, et al. "The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the Non-Motor Symptoms of Parkinson's Disease." *Move Disord* 26 (2011): 42-80.
- Joseph T DiPiro, Robert L Talbert, Gary C Yee and Gary R Matzke, et al. "Book Review: Pharmacotherapy: A Pathophysiologic Approach, 7th Edition." *Ann Pharmacother* 43 (2009): 395.
- Scott J. Kutscher, Siavash F arshidpanah and Daniel O. Claassen. "Sleep Dysfunction and Its Management in Parkinson's Disease." *Curr Treat Options Neurol* 16 (2014): 304.
- Aleksandar Videnovic, Charleston Noble, Kathryn J. Reid and Jie Peng, et al. "Circadian Melatonin Rhythm and Excessive Daytime Sleepiness in Parkinson Disease." *JAMA Neurol* 71 (2014): 463-469.
- Inara F. Raupp-Barcaro, Maria A. Vital, José C. Galduróz and Roberto Andreatini. "Potential Antidepressant Effect of Amantadine: A Review of Preclinical Studies and Clinical Trials." *Braz J Psychiat* 40 (2018): 449-458.
- Fred Y. Aoki and Daniel S. Sitar. "Clinical Pharmacokinetics of Amantadine Hydrochloride." *Clin Pharmacokinet* 14 (1988): 35-51.
- Michael Shuman, Athena Chukwu, Nathan Van Veldhuizen and Steven A. Miller. "Relationship between Mirtazapine Dose and Incidence of Adrenergic Side Effects: An Exploratory Analysis." *Ment Health Clin* 9 (2019): 41-47.
- Leonard Sasada and Karlamangla Atsushi. "Dose-Dependent Sedating and Stimulating Effects of Mirtazapine." *Proc UCLA Health* 19 (2015): 1-2.
- Paul K. Whelton, Robert M. Carey, Wilbert S. Aronow and Donald E. Casey, et al. "ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." *J Am Coll Cardiol* 71 (2015): 1269-1324.
- Denise C. Jarrin, Pasquale K. Alvaro, Marc-André Bouchard and Stephanie D. Jarrin, et al. "Insomnia and Hypertension: A Systematic Review." *Sleep Med* 41 (2017): 3-38.
- Glenna A. Dowling, Judith Mastick, Eric Colling and Julie H. Carter, et al. "Melatonin for Sleep Disturbances in Parkinson's Disease." *Sleep Med* 6 (2005): 459-466.
- Campbell Partonen, Miller Avery and Woesner Mackert. "Bright Light Therapy: Seasonal Affective Disorder and Beyond." *Einstein J Biol Med* 32 (2017): 13-25.

How to cite this article: Meghan Ha, Nishita S. Amin, Katie Meyers, and Jacques Turgeon, et al. "Balancing Sleep and Motor Symptoms: A Case Report of Managing Insomnia in Parkinson's Disease." *Clin Case Rep* 11 (2021): 1432.