

Morning akinesia in Parkinson's disease: challenges and solutions

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Abstract: Motor complications of Parkinson's disease (PD) have been reported to occur after a few years of treatment with levodopa (L-dopa). Morning akinesia is a delayed ON of the first L-dopa daily dose, occurring in almost 60% of patients on dopaminergic treatment. This is primarily a motor symptom, but has been recently recognized as being correlated with nonmotor fluctuations. Sleep disorders and gastrointestinal dysfunction might be the underlying mechanisms. Over the past 30 years, several pharmacological and nonpharmacological approaches have been investigated.

Keywords: Parkinson's disease, morning akinesia, motor fluctuation, L-dopa

Introduction

Most patients with Parkinson's disease (PD) on levodopa (L-dopa) have motor fluctuations. An improvement in symptoms after L-dopa administration is defined as "ON", whereas a return to symptoms is termed "OFF",¹ ie, when L-dopa (L-dopa) plasma concentration decreases. OFF periods generally appear when the benefit from a given L-dopa dose disappears prematurely (wearing OFF) or when the next L-dopa dose produces a delayed onset of action (delayed ON).^{2,3} Delayed ON of the first L-dopa daily dose is known as morning akinesia, and this condition can significantly affect the quality of life (QoL) and impair daily activities, such as arising from bed, dressing, bathing, toileting, preparing breakfast, and getting on with the day's work.² Morning akinesia is the most common, and often, the first motor complication of PD.² It is noticed at awakening after a nightlong treatment-free period, reflecting the dopaminergic nocturnal decline with insufficient nighttime storage or refreshing of the dopaminergic system during nighttime and sleep.

Over the past 3 decades, several investigations have been carried out to understand this symptomatology.

Pathophysiology

Morning akinesia occurs in almost 60% of PD patients on dopaminergic treatment across all disease stages.³ Most of these patients have experienced longer durations of PD motor symptoms and are in moderate to advanced stages of disease, with the largest proportion of these patients classified according to the Hoehn and Yahr scale 2.5–3).³

OFF periods are mainly characterized by motor symptoms and motor complications, although they have been recently attributed to nonmotor OFF and nonmotor fluctuations.^{3,4}

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The optimization of dopaminergic treatment is also crucial. Peripheral and central factors underlie these fluctuations.

The emerging role of nonmotor aspects

Nonmotor symptoms (NMSs) are often poorly understood and inadequately treated, but are thought to arise from a more diffused involvement of the central, autonomic, and enteric nervous systems.⁵

The relevance of NMSs has recently been studied in 320 PD patients,³ with 88% of the patients reporting an association between morning akinesia and NMSs.

The predominant NMSs associated with morning akinesia are urgency of urination, anxiety, dribbling of saliva, pain, low mood, limb paresthesia, and dizziness.

Sleep disorders are often involved in triggering early morning OFF periods. PD patients have been reported to have reduced total sleep times compared to healthy controls.⁶ Sleep efficiency is often reduced, with an increased number of awakenings and an increased wakefulness after sleep onset. Sleep fragmentation is the most consistent and often the earliest sleep disturbance in PD, with frequent awakenings during the night, with often 30–40% of the time being awake. Up to 80% of PD patients report having 2–5 awakenings per night.^{7,8} Sleep disruption, thus, may easily promote the appearance of nightlong rigidity and prolonged muscle contractions.

The role of sleep in early morning motor disturbances has not yet been clarified. In a recent study, 10–55% of patients with mild to moderate PD and a fluctuating response to L-dopa experienced a reduction in disability for 40–60 minutes after waking.⁹ This improvement before drug intake is known as sleep benefit, and may be due to an improvement in dopaminergic function during sleep. Other “pharmacologic hypotheses” implicate drug-induced motor fluctuations,⁷ transient worsening after the first morning L-dopa dose,¹⁰ and a competition between large neutral amino acids and L-dopa for transport access into the brain.^{8,11}

Other symptoms have been recently associated with morning akinesia, including post-prandial bloating, abdominal discomfort, early satiety, nausea, vomiting, weight loss, and malnutrition,^{12,13} or in other words, gastroparesis is a consistent feature of gastrointestinal dysfunction (GID).¹⁴

GID in PD is due to both the underlying synucleinopathy and dopaminergic therapy.¹⁵ Data suggest that the underlying neurodegenerative process affects the central, autonomic, and enteric nervous systems. Features of GID include dry mouth,

sialorrhoea, dysphagia, oesophageal dysmotility, gastro-oesophageal reflux, gastroparesis, constipation, and impaired defecation.¹² These gastrointestinal symptoms significantly impair QoL in PD.¹⁶

Gastroparesis, a condition where the stomach takes longer than normal to empty, is common in both early and advanced PD patients, and may even be a marker of preclinical PD.¹⁷ Nonetheless, data concerning prevalence, relationship to the underlying disease process, relevance to PD management, and optimal treatment of gastroparetic symptoms are still limited.¹³ In addition to causing gastrointestinal symptoms, gastroparesis may cause motor fluctuations, including delayed ON and morning akinesia, by delaying the arrival of oral L-dopa to intestinal absorptive sites.^{12,14,18–21}

To guarantee a high level of efficacy from oral L-dopa, it must be taken on an empty stomach so that it can be absorbed into the proximal small intestine. Gastroparesis can cause a delay in L-dopa delivery to the duodenum, resulting in the clinical phenomenon of delayed ON after a L-dopa dose.¹⁸ Several studies have demonstrated a significant relationship between gastric emptying and L-dopa pharmacokinetics in PD patients, suggesting that delayed gastric emptying contributes to delayed ON and other motor fluctuations.^{22–24}

Other drugs, including dopamine agonists, anticholinergics, amantadine, inhibitors of monoamine oxidase and catechol-O-methyltransferase (COMT), may also contribute to GID.²⁵ L-dopa can increase gastric acid secretion, impair gastric relaxation, and delay gastric emptying;^{14,26,27} anticholinergics and amantadine commonly cause dry mouth and constipation; and COMT inhibitors can cause diarrhoea.

The association between morning akinesia and other common NMSs which strongly impair health-related QoL, such as fatigue, pain, and psychiatric disturbances,⁴ needs to be investigated. Nevertheless, improving NMSs should be viewed as an important part in the management of PD.^{4,28}

It has also been shown that regardless of the disease duration or severity of motor complications, not a single NMS but the burden of “total” NMSs is the major determinant of QoL.²⁸ Some symptoms such as fatigue, depression, and concentration problems seem to contribute to this burden more than others, since these occur both in “ON” and “OFF” periods. Fatigue has emerged as a key NMS of PD, and its prevalence reached almost 50% even in patients with early PD.⁴

Challenges and solutions

Since the first descriptions of L-dopa-induced complications,^{29,30} delayed ON, sleep disorders, and early morning OFF periods have always been controversial issues. Specifically,

the optimization of traditional pharmacologic PD oral therapy by itself may not be sufficient for alleviating symptoms.

Although it has been reported that 50% to 80% of PD patients develop motor complications within 5 to 10 years from the beginning of L-dopa therapy,²⁹ recent studies state that ~50% of patients show motor complications within 2 years of treatment.^{31,32}

Standard oral L-dopa treatment is inadequate for the treatment of morning akinesia for reasons related to its pharmacodynamics and pharmacokinetics and because have a short half-life, erratic gastrointestinal absorption, and competitive transport across the blood–brain barrier.

L-dopa has a very poor solubility and its “end-of-dose” deterioration is directly related to the level of plasma L-dopa. Therefore, one of the first strategies attempted to focus on prolonging L-dopa plasma levels, using long-acting, controlled-release L-dopa preparations.^{33–36} Nevertheless, due to delayed gastric emptying, an oral dose of L-dopa may remain in the stomach for a long time before being absorbed in the small intestine.^{33–36}

Another approach is administering L-dopa as a liquid solution to reduce gastric transit time and improve the onset of effect. This approach may be beneficial for some patients with severe fluctuations; however, the clinical benefits of liquid L-dopa compared with tablets has not been confirmed in controlled clinical studies.³⁷ To manage early morning akinesia and episodes of nocturnal hypomobility, many patients use L-dopa on an intermittent or as-needed basis. However, the slow or unpredictable onset of effect limits the clinical benefit.³⁸

The addition of monoamine oxidase-B inhibitors and COMT inhibitors may be helpful in prolonging the duration of the efficacy of each single L-dopa dose.^{34,39,40}

In addition to absorption delay due to slowed gastrointestinal transit, circulating diet-derived proteins may interfere with the transit of L-dopa across the blood–brain barrier and in the gut.^{38,41–43} Dietary manipulation, such as reducing the ingestion of protein to minimize L-dopa-protein competition across cellular membrane transporters, may be attempted.^{35,44} Multiple small meals with low fat content and a reduction in the intake of indigestible fiber are considered as effective nonpharmacological strategies for management of gastroparesis. If possible, medications that can slow gastric emptying should be avoided.

Pharmacological treatment of gastroparesis includes the use of prokinetic agents. Dopamine antagonists, such as domperidone and metoclopramide, can also reduce gastric emptying time. Compared to metoclopramide, domperidone does not cross the blood–brain barrier, consequently having

minimal effects on the central nervous system, while at the same time significantly improving gastric emptying without affecting PD motor symptoms.^{14,25,27}

Long-acting dopamine agonists allow more stable and continuous dopaminergic stimulation (CDS) and improve nocturnal disability. In previous studies, cabergoline, in particular, appeared to be more effective than the L-dopa controlled-release formulation in relieving nocturnal painful dystonia, nocturnal and morning akinesia, and early morning dystonia.^{45–48} Surprisingly, this improvement was associated with a significant increase in the number of awakenings and stage shifts, as shown by polysomnography. The functional significance of this finding remains uncertain⁴⁹ (Table 1).

Bromocriptine, in combination with lower doses of L-dopa, resulted in therapeutic response equal to that achieved with high-dose L-dopa alone, but with significantly fewer end-of-dose failures and dyskinesia. At the end of 5 years, early combination of L-dopa and bromocriptine resulted in a reduced frequency of early morning akinesia and dose-related freezing of gait episodes.^{50,51}

More recently, continuous 24-hour delivery of a dopamine agonist has been reported as an attractive option for the management of PD patients with end-of-dose symptom deterioration and specific complaints of nocturnal and early morning motor impairment.⁵²

Moreover, prolonged release of dopamine agonists medications (rotigotine, ropinirole, pramipexole) has been associated with significantly less early morning OFF periods compared with L-dopa therapy only.³

In 2010, the RECOVER study, a large-scale, double-blind, randomized trial reported 24-hour transdermal rotigotine treatment to be associated with significant benefits versus placebo in the management of early morning motor impairment and nocturnal sleep disturbances. Rotigotine was also associated with improvements in nighttime disabilities (such as limb restlessness, immobility, pain, and cramps), and possibly dopaminergic nonmotor daytime symptoms (such as fatigue and mood) as well.⁵³ In addition, the transdermal route bypasses the gastrointestinal tract and its associated motor fluctuations.

An improvement in sleep associated with rotigotine may be the result of its effect on curbing nocturnal motor symptoms: limb restlessness, urge to move arms or legs, painful posturing in the morning, and tremor on awakening. Likewise, reported improvement in painful posturing in the morning may be the result of an early morning improvement in akinesia and dystonia.⁵³ Moreover, transdermal rotigotine demonstrated efficacy and safety as monotherapy in early PD and in reducing “OFF” hours in L-dopa-treated patients with advanced PD.^{54,55}

Table 1 Studies on the treatments managing morning akinesia

Authors	Proposed treatments	Pros	Cons
Baas and Schueler ⁴⁵ Högl et al ⁴⁹	Cabergoline	More effective than the CR-L-dopa in relieving nocturnal painful dystonia, nocturnal and morning akinesia, and early morning dystonia	Increase in the number of awakenings and stage shifts, and ergot-derived drug adverse events
Rinne ⁵⁰ Rinne ⁵¹	Bromocriptine + L-dopa	Reduced frequency of early morning akinesia and dose-related freezing of gait episodes	Ergot-derived drug adverse events
Giladi et al ⁵² Trenkwalder et al ⁵³	Rotigotine	Benefit in early morning motor impairment and sleep disturbances; transdermal administration	Primes/worsens dyskinesia; ICD; cutaneous reactions
Chaudhuri et al ⁵⁶ Poewe et al ⁵⁷	Mirapexin and ropinirole	Improvements in sleep disturbances	Primes/worsens dyskinesia; reduced absorption due to oral administration
Trosch et al ⁵⁸ Pfeiffer et al ⁵⁹	Apomorphine	Rapid and reliable time-to-ON in patients with morning akinesia	Self- administration of subcutaneous injection
Zibetti et al ⁶¹	LCIG	Improvement of nocturnal sleep quality, pain, muscle cramps, restlessness, and painful posturing in the morning	High costs, patients selection, surgical risks
Arnulf et al ⁶² Hjort et al ⁶³ Derrey et al ⁶⁴	STN DBS	Improvement of sleep architecture and quality; alleviation of "OFF period" dystonia after microlesion effect produced by surgical intervention	High costs, patients selection, surgical risks

Abbreviations: L-dopa, levodopa; CR-L-dopa, controlled release levodopa; LCIG, levodopa/carbidopa intestinal gel; STN DBS, subthalamic nuclei deep brain stimulation; ICD, impulse control disorder.

Significant improvements in sleep disturbances have also been recorded with prolonged-release formulations of ropinirole^{54,56} and pramipexole.^{54,57} Though these medications have shown their efficacy and safety in advanced PD,^{56,57} like L-dopa, they are administered orally and their capacity of inducing motor complication is low. In fact, as with all dopaminergic drugs, they may trigger the onset or worsen dyskinesias.⁴⁰

Apomorphine is a potent short-acting dopamine D1 and D2 receptor agonist that can be administered subcutaneously and is currently being used for the management of sudden, unexpected and refractory L-dopa-induced OFF states in fluctuating PD either as intermittent rescue injections or continuous infusions.^{58–60} Apomorphine injections may be helpful in treating morning akinesia, since time-to-ON should not be affected by delayed gastric emptying due to gastroparesis. The ongoing Phase IV, multicenter, open-label AM-IMPAKT trial is investigating whether subcutaneous apomorphine injection on awakening can provide improvement in motor and NMSs in PD patients with morning akinesia. Interim results suggest that apomorphine injection as an adjunctive therapy may provide a rapid and reliable time-to-ON in patients with morning akinesia, resulting in significant improvements in QoL^{3,14} (Table 1).

CDS is a valid strategy in controlling both motor and NMSs in PD. A recent study on a small number of patients reported that subjective measures of sleep quality improved

substantially with L-dopa/carbidopa intestinal gel (LCIG) infusion in advanced PD. Additionally, nocturnal sleep improved in all patients treated with LCIG compared with previous oral therapy. In particular, ameliorations in nocturnal sleep quality, pain, muscle cramps, restlessness, and painful posturing in the morning were reported.⁶¹

Another small study reported improvements in sleep architecture and quality, along with an increase in total sleep time (up to 47%) even in patients treated with subthalamic nuclei (STN) deep brain stimulation (DBS).^{62,63} Moreover, an alleviation of "OFF" dystonia was registered after the microlesion effect produced by STN DBS surgical intervention. In this group of 30 patients, the morning of the third day following STN implantation, after at least a 12-hour withdrawal of dopaminergic treatment and before the programmable pulse generator was switched on, a significant clinical improvement was observed.⁶⁴ Motor score of Unified Parkinson's Disease Rating Scale improved by 27% and 12 patients reported complete relief of their symptoms in the immediate postoperative period, remaining free of painful off-period dystonia throughout the 6-month follow-up period.⁶⁴

Yet, larger and more specific studies performed over longer periods of time are needed to fully evaluate the beneficial effects of LCIG therapy and STN DBS on both sleep and early morning dystonia.

Discussion

Morning akinesia is one of the most common and earliest motor complications in PD patients, affecting almost all stages of the disease. Its physiopathology is complex and even if the fluctuations of L-dopa levels in plasma can be considered as the primary trigger, nondopaminergic pathways are also believed to play underlying roles in both its maintenance and often unpredictable manifestation.

Delayed time-to-ON after the first L-dopa dose has been studied and addressed in many different ways. Optimizing dose and timing of standard L-dopa plus controlled-release L-dopa formulations alone before sleep may offer benefit. Moreover, low-protein, low-fat multiple small meals during the day may help speed up gastric transit along with a prokinetic regimen, such as domperidone. Liquid L-dopa formulations may lead to a faster intestinal absorption without compromising the benefit associated with tablets.

Prompt analyses of other NMSs, such as sleep disorders, should be performed. Insomnia and sleep fragmentation are known to worsen early morning motor functions and prolong time-to-ON. Recommendations concerning sleep hygiene and behavioural therapy^{65,66} may be sufficient to improve QoL.

Prolonged-release dopamine agonist add-on treatments can provide a continuous, more physiologic dopaminergic stimulation, along with improvements in NMSs including sleep disorders.

Small doses of subcutaneous apomorphine, when administered as needed, can rapidly reverse OFF states. However, an early morning subcutaneous self-pen injection in disabled advanced PD patients could be troublesome. Limited evidence is available for ameliorating sleep disorders and early morning motor functions with CDS by LCIG and STN DBS.

The dopaminergic oral treatment alone has been reported^{3,23,54} to be inadequate in providing benefit for morning akinesia. A treatment based on a more continuous stimulation could improve this benefit. Specifically, a continuous stimulation would lead to a sustained delivery of treatment over time.

Disclosure

The authors report no conflicts of interest in this work.

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