

Letter

Turning Back the Clock in Parkinson's Disease: Practical Recommendations for Managing Diurnal Symptom Worsening

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Dear Sirs,

With great interest we read the research paper by Van Wamelen and colleagues on diurnal motor patterns in persons with de novo Parkinson's disease [1]. They present further evidence for the influence of the 'biological master clock' (BMC) on the motor symptoms of Parkinson's disease. Previously, this same group already demonstrated a circannual pattern in non-motor symptoms [2].

In addition to the valuable work provided in these original publications, we would like to add a number of complementary clinical considerations to indicate that there are further and, importantly, potentially modifiable reasons why Parkinson's disease patients may experience a worsening of motor and non-motor symptoms during the course of the day. Moreover, we add some practical recommendations for identifying and managing these various causes of diurnal patterns in daily practice, as outlined in Table 1.

The relative importance of the factors mentioned in the table may differ between patients in relatively early disease stages (lower Hoehn & Yahr stages) and those with more advanced disease (higher Hoehn & Yahr stages). For example, a normal (BMC-related) diurnal pattern might play a greater role in de novo patients [1] whilst fatigue and pharmacological factors are presumably more significant in patients with more advanced disease [4, 5]. There is also a difference in explanatory mechanisms and clinical approach between untreated de novo patients, versus patients who are treated with symptomatic dopaminergic medication, in particular those experiencing response fluctuations.

Most recommendations outlined in the table are self-explanatory. However, the non-pharmacological management of fatigue may warrant some further clarification. It has long been standard practice to refer patients with chronic and progressive neurological disorders experiencing fatigue to an occupational therapist, aiming to deploy strategies on how to make optimal use of the available energy during the day. This treatment approach has been referred to as *energy conservation management* (ECM). However,

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Table 1
BMC-related and non-BMC-related causes and possible interventions for diurnal patterns in symptoms of Parkinson's disease

Cause	Possible interventions
Circadian rhythm disruption	<ul style="list-style-type: none"> • Melatonin [3] • Exercise [3] • Bright-light therapy [3]
Fatigue	<ul style="list-style-type: none"> • Ensure adequate nocturnal sleep quality and quantity (consider e.g., RLS, RBD, nocturnal <i>OFF</i> periods, nocturia, OSAS) • Rule out and treat other causes (e.g., use of beta blockers, benzodiazepines, vitamin deficiency, hypothyroidism, anemia) • Refer to occupational therapist (scheduling of daily activities depending on individual energy levels) • Take extra (dispersible) L-DOPA prior to scheduled exercise activities • Refer to psychologist for cognitive behavioral therapy (see text for details) • Rasagiline [6] • Scheduled early-afternoon power naps [7]
Waning of night-time sleep benefit [7]	<p><i>In patients experiencing no night-time sleep benefit, consider sleep study and ensure a good night-time sleep quality and quantity (see fatigue section)</i></p>
Impaired L-DOPA absorption in the gut [8, 9], peripheral breakdown of L-DOPA [10], and increase in intestinal / plasma large neutral amino acids [11]	<ul style="list-style-type: none"> • Management of gastrointestinal dysmotility [8], constipation [8], and protein intake [12] • Identify and treat HPI and SIBO [9] • Switch to non-enteral dopaminergic medication (e.g., transdermal rotigotine or apomorphine subcutaneously)
Repeated-dose dependent reduction of response to dopaminergic stimulation [13–15]	<ul style="list-style-type: none"> • Reduce dosing frequency using long-acting dopamine agonists, extended-release L-DOPA, COMT inhibitors, continuous subcutaneous apomorphine infusion
Dose accumulation resulting in high-dopa dyskinesias with a diurnal pattern [16]	<ul style="list-style-type: none"> • Management of gastrointestinal dysmotility [8], constipation [8] and protein intake [12] • Identification and cessation of injudicious use of extended-release L-DOPA preparations [16] • Reducing total dopamine dose and replacing with long-acting agonists with a net lower LED
Evening low-dopa dyskinesias [17]	<ul style="list-style-type: none"> • Short-acting dopamine agonist [17] • More frequent, lower L-DOPA doses [17] • Deep brain stimulation [18] <p><i>Might prove difficult to treat, being a pharmacodynamic phenomenon</i></p>

HPI, Helicobacter pylori infection; LED, L-DOPA equivalent dose; OSAS, obstructive sleep apnea syndrome; RLS, restless-legs syndrome; RBD, REM-sleep behavior disorder; SIBO, small intestinal bacterial overgrowth.

recent research in patients with multiple sclerosis (MS) demonstrated that this therapy does not significantly improve fatigue, and that cognitive behavioral therapy (aimed at acceptance of the fatigue level and systematically increasing activity, rather than adapting activities to the fatigue level, as is done in ECM) works better in improving daytime energy levels [19]. This approach may apply to persons living with Parkinson's disease as well, given that one of the hypothesized mechanisms of MS-related fatigue is a dopaminergic deficit, which could explain the efficacy of amantadine for fatigue in some MS patients [20].

Of note, the reverse effect, patients functioning *worse* in the morning, may be observed in patients suffering from supine hypertension combined with orthostatic hypotension, a combination often seen as part of autonomic dysfunction in advanced Parkinson's disease [21]. The troughs in blood pressure

resulting from orthostatic hypotension are typically most pronounced in the morning, not too long after rising from the bed.

Recognition of diurnal patterns, as was emphasized again by the important findings of Van Wamelen and colleagues, may lead to the following practical recommendations: (1) whenever possible, plan your assessment of Parkinson's disease patients in the morning to reduce the burden for patients and also to obtain a representative impression of their best motor performance; otherwise at least plan your assessment at a consistent time during the day, to allow for a more reliable comparison between subsequent visits; (2) in the framework of clinical trials, repeated measures should ideally be performed at the same time of day (and for longer-lasting studies, in the same season); (3) identify and treat non-BMC related causes of diurnal fluctuations, using table 1 for guidance; and (4) if a circadian rhythm disturbance is suspected as a cause

of BMC-related diurnal fluctuations, try to treat this accordingly [22].

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CONFLICT OF INTEREST

None of the authors has any relevant disclosures to make.

REFERENCES

- [1] van Wamelen DJ, Urso D, Chaudhuri KR (2021) How time rules: Diurnal motor patterns in de novo Parkinson's disease. *J Parkinsons Dis*, doi: 10.3233/JPD-202352.
- [2] van Wamelen DJ, Podlewska AM, Leta V, Śmiłowska K, Rizos A, Martinez-Martin P, Bloem BR, Chaudhuri KR (2019) Slave to the rhythm: Seasonal differences in non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord* **63**, 73-76.
- [3] Kutscher SJ, Farshidpanah S, Claassen DO (2014) Sleep dysfunction and its management in Parkinson's disease. *Curr Treat Options Neurol* **16**, 304.
- [4] Solla P, Cannas A, Mulas CS, Perra S, Corona A, Bas-sareo PP, Marrosu F (2014) Association between fatigue and other motor and non-motor symptoms in Parkinson's disease patients. *J Neurol* **261**, 382-391.
- [5] Valko PO, Waldvogel D, Weller M, Bassetti CL, Held U, Baumann CR (2010) Fatigue and excessive daytime sleepiness in idiopathic Parkinson's disease differently correlate with motor symptoms, depression and dopaminergic treatment. *Eur J Neurol* **17**, 1428-1436.
- [6] Elbers RG, Verhoef J, van Wegen EE, Berendse HW, Kwakkel G (2015) Interventions for fatigue in Parkinson's disease. *Cochrane Database Syst Rev*, CD010925.
- [7] van Gilst MM, Bloem BR, Overeem S (2013) "Sleep benefit" in Parkinson's disease: A systematic review. *Parkinsonism Relat Disord* **19**, 654-659.
- [8] Mukherjee A, Biswas A, Das SK (2016) Gut dysfunction in Parkinson's disease. *World J Gastroenterol* **22**, 5742-5752.
- [9] Fasano A, Bove F, Gabrielli M, Petracca M, Zocco MA, Ragazzoni E, Barbaro F, Piano C, Fortuna S, Tortora A, Di Giacomo R, Campanale M, Gigante G, Lauritano EC, Navarra P, Marconi S, Gasbarrini A, Bentivoglio AR (2013) The role of small intestinal bacterial overgrowth in Parkinson's disease. *Mov Disord* **28**, 1241-1249.
- [10] van Rumund A, Pavelka L, Esselink RAJ, Geurtz BPM, Wevers RA, Mollenhauer B, Krüger R, Bloem BR, Verbeek MM (2021) Peripheral decarboxylase inhibitors paradoxically induce aromatic L-amino acid decarboxylase. *NPJ Parkinson's Disease* **7**, 29.
- [11] Nutt JG, Holford NH (1996) The response to levodopa in Parkinson's disease: Imposing pharmacological law and order. *Ann Neurol* **39**, 561-573.
- [12] Wang L, Xiong N, Huang J, Guo S, Liu L, Han C, Zhang G, Jiang H, Ma K, Xia Y, Xu X, Li J, Liu JY, Wang T (2017) Protein-restricted diets for ameliorating motor fluctuations in Parkinson's disease. *Front Aging Neurosci* **9**, 206.
- [13] Monge A, Viselli F, Stocchi F, Barbato L, Bolner A, Modugno N, Paradiso M, Ruggieri S, Nordera G (2004) Variation in the dopaminergic response during the day in Parkinson disease. *Clin Neuropharmacol* **27**, 116-118.
- [14] Bonuccelli U, Del Dotto P, Lucetti C, Petrozzi L, Bernardini S, Gambaccini G, Rossi G, Piccini P (2000) Diurnal motor variations to repeated doses of levodopa in Parkinson's disease. *Clin Neuropharmacol* **23**, 28-33.
- [15] Piccini P, Del Dotto P, Pardini C, D'Antonio P, Rossi G, Bonuccelli U (1991) [Diurnal worsening in Parkinson patients treated with levodopa]. *Riv Neurol* **61**, 219-224.
- [16] Rodnitzky RL (1992) The use of Sinemet CR in the management of mild to moderate Parkinson's disease. *Neurology* **42**, 44-50; discussion 57-60.
- [17] Zimmerman TR, Jr., Sage JI, Lang AE, Mark MH (1994) Severe evening dyskinesias in advanced Parkinson's disease: Clinical description, relation to plasma levodopa, and treatment. *Mov Disord* **9**, 173-177.
- [18] Apetauerova D, Ryan RK, Ro SI, Arle J, Shils J, Papavasiliou E, Tarsy D (2006) End of day dyskinesia in advanced Parkinson's disease can be eliminated by bilateral subthalamic nucleus or globus pallidus deep brain stimulation. *Mov Disord* **21**, 1277-1279.
- [19] De Gier M, Beckerman H, Knoop H, De Groot V (2020) Behandeling van MS-gerelateerde vermoeidheid: Recente inzichten. *Tijdschrift Neurol Neurochir* **121**, 236-241.
- [20] MacAllister WS, Krupp LB (2005) Multiple sclerosis-related fatigue. *Phys Med Rehabil Clin N Am* **16**, 483-502.
- [21] Tulbă; D, Cozma L, Bălănescu P, Buzea A, Băicuș C, Popescu BO (2021) Blood pressure patterns in patients with Parkinson's disease: A systematic review. *J Pers Med* **11**, 129.
- [22] Stewart J, Bachman G, Cooper C, Liu L, Ancoli-Israel S, Alibiglou L (2018) Circadian dysfunction and fluctuations in gait initiation impairment in Parkinson's disease. *Exp Brain Res* **236**, 655-664.