ISSN: 3065-5145
Case Report
Journal of Clinical Case Studies and Family Medicine

AI-Augmented Management of Pharmacoresistant Insomnia and Restless Legs Syndrome in Park2 Parkinson's Disease: an N-OF-1 Case Report Integrating Pharmacogenetics, Chronopharmacology, Digital Monitoring, and an LLM Co-Pilot

Stefano Scapigliati[1]*, & Sabina De Innocentiis, PhD[2]

[1]*Department of Engineering Science, Guglielmo Marconi University, Rome, Italy*
[2]*Institute for Environmental Protection and Research (ISPRA), Rome, Italy*

***Corresponding author:** Stefano Scapigliati, Department of Engineering Science, Guglielmo Marconi University, Rome, Italy.

Submitted: 26 February 2026 **Accepted:** 05 March 2026 **Published:** 12 March 2026

Citation: *Scapigliati, S., De Innocentiis, S. (2026).AI-Augmented Management OF Pharmacoresistant Insomnia and Restless Legs Syndrome in Park2 Parkinson's Disease: an N-OF-1 Case Report Integrating Pharmacogenetics, Chronopharmacology, Digital Monitoring, and an LLM Co-Pilot. J of Clin Case Stu Fam Med, 2(2), 01-07.*

Abstract

We report a case of young-onset PARK2 Parkinson's disease complicated by severe, persistent insomnia, restless legs syndrome (RLS), and REM sleep behavior disorder (RBD), refractory to multiple conventional strategies. The clinical course included features consistent with levodopa-related rebound and augmentation, culminating in a systemic crisis with near-total sleep deprivation and night eating syndrome (NES). An N-of-1 precision approach was implemented by combining pharmacogenetics, molecule- and time- specific repositioning of medications (chronopharmacology), and continuous monitoring using consumer wearable sleep metrics and continuous glucose monitoring (CGM). Crucially, the optimization was conducted within an iterative human–AI loop in which a large language model (LLM) acted as a cognitive co-pilot to integrate multiplexed data streams, surface interaction risks, and generate prioritized hypotheses that were then clinically validated and implemented under continuous neurologist supervision. Key steps included discontinuation of evening levodopa, a strict pre-dinner 'gastric-sparing' window on an empty stomach to optimize absorption, and an evening synergy between low-dose pramipexole, pregabalin, and clonazepam. From September 2025 to February 2026, monthly wearable estimates showed deep sleep increasing from 5–8 min to 42–43 min and REM sleep increasing from 7–10 min to 45–50 min. In parallel, metabolic markers improved (HbA1c 7.2% to 6.8%, ALT/GPT 61 to 34 U/L within 12 months), with a 3 kg weight loss. This case illustrates a pragmatic framework for AI-augmented clinical reasoning in a complex multimorbid patient, demonstrating a path from pharmacoresistance to sustained clinical improvement.

Keywords: Parkinson's Disease, PARK2, Insomnia, Restless Legs Syndrome, REM Sleep Behavior Disorder, Chronopharmacology, Pharmacogenetics, Continuous Glucose Monitoring, Wearables, Large Language Model.

Introduction

Sleep disorders are a pervasive and disabling non-motor feature of Parkinson's disease (PD), profoundly impacting quality of life [1, 2]. The spectrum includes insomnia, restless legs syndrome (RLS) or Willis-Ekbom disease, and REM sleep behavior disorder (RBD), which are particularly frequent and challenging to manage [3, 4]. The therapeutic challenge is amplified in patients with young-onset genetic forms, such as those associated with PARK2 gene mutations, where non-motor phenomenology can be complex and intertwined with severe systemic comorbidities [1]. Standard therapeutic approaches, often centered on dopaminergic replacement for motor control, can paradoxically exacerbate sleep disturbances. Evening administration of levodopa, for instance, may worsen nocturnal symptoms through end-of- dose rebound or induce augmentation, a long-term iatrogenic worsening of RLS [5]. Furthermore, metabolic comorbidities like type 2 diabetes and the use of incretin-based therapies (e.g., GLP-1 receptor agonists) can interfere with evening drug absorption via

delayed gastric emptying, impacting both sleep continuity and nocturnal glucose stability [10]. While these mechanisms are individually recognized, their real-time intersection in a single patient can be difficult to operationalize during standard episodic clinical encounters.

This N-of-1 case report describes a precision medicine strategy developed for a patient with PARK2 PD whose life was dominated by pharmacoresistant insomnia and severe RLS, culminating in a systemic crisis. After numerous therapeutic failures with conventional protocols, we implemented an integrated approach combining pharmacogenetics, chronopharmacology, and data-driven pharmacological synergy, augmented by an AI co-pilot for complex data synthesis. The objective is to illustrate the analytical pathway and methodology that resolved a seemingly intractable clinical picture by shifting the focus from symptomatic treatment to correcting underlying biochemical and pharmacokinetic mechanisms.

Case Presentation

Patient Information and Clinical History

The patient is a 56-year-old male with a diagnosis of young-onset PD (diagnosed in 2009), subsequently confirmed to be associated with a PARK2 gene mutation. The clinical picture was complicated by a constellation of severe sleep disorders and significant systemic comorbidities, as summarized in Table 1.

Table 1: The patient (also the first author) provided written informed consent for the publication of this report and de-identified data sharing

Category	Description
Patient	Male, 56 years old
Primary Neurological Diagnosis	Parkinson's Disease (diagnosed 2009), PARK2 gene mutation
Associated Sleep Disorders	Chronic pharmacoresistant insomnia, Restless Legs Syndrome (RLS), REM Sleep Behavior Disorder (RBD)
Relevant Comorbidities	Chronic ischemic heart disease (3 coronary stents), Type 2 Diabetes Mellitus, Arterial Hypertension, Class I Obesity, Diverticulosis, Cervicobrachialgia, Bilateral complete rotator cuff tear
Metabolic Management	Tirzepatide (GLP-1/GIP receptor agonist) 7.5 mg/week for glycemic control and weight management

History of Therapeutic Failures

The patient's therapeutic journey was marked by a long series of failures that progressively worsened his clinical condition. Initial attempts to manage insomnia with standard benzodiazepines (e.g., diazepam, bromazepam) were ineffective even at high doses, instead producing paradoxical reactions such as sleepwalking and complex parasomnias. This idiosyncratic response was later explained by pharmacogenomic testing (MIFAR test), which identified the patient as an intermediate metabolizer for the CYP2C19 enzyme, a primary metabolic pathway for diazepam [11].

This genetic profile likely led to altered drug bioavailability and accumulation, providing a scientific basis for the observed inefficacy and toxicity. The management of RLS and motor symptoms with dopaminergic drugs proved to be a double-edged sword. The use of levodopa, particularly with afternoon and evening doses, triggered two deleterious phenomena: augmentation, a paradoxical worsening of RLS characterized by earlier symptom onset and increased intensity, and nocturnal rebound, where the short half-life of levodopa led to a dopaminergic "crash" during the night, causing a violent explosion of RLS symptoms (Figure 1).

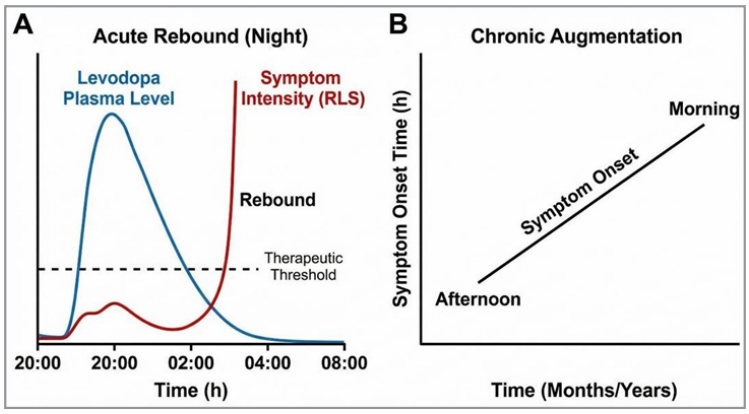

Figure 1: The Dopaminergic Paradox: Rebound and Augmentation

Panel A illustrates the acute "rebound" effect, where a rapid drop in levodopa plasma levels below the therapeutic threshold triggers a severe spike in RLS symptoms during the night. Panel B illustrates the chronic "augmentation" effect, where, over months, the onset of RLS symptoms shifts progressively earlier in the day.The crisis culminated in an episode of ten consecutive days of total sleep deprivation.

This state of "forced wakefulness" triggered a cascade of systemic consequences, including the activation of Night Eating Syndrome (NES), with a devastating impact on glycemic control and obesity. A vicious cycle was established where chronic insomnia, nocturnal eating, and metabolic dysregulation mutually reinforced each other, bringing the patient to a physical and psychological breaking point.

Methods

N-of-1 Study Design and Outcomes

A prospective N-of-1 optimization was conducted with stepwise changes and pre-defined outcomes. Primary outcomes were total sleep time, sleep continuity (awakenings), and wearable-derived estimates of deep sleep and REM sleep. Given the known limitations of consumer devices for sleep staging [12, 13], these estimates were treated as intra-individual trend indicators rather than polysomnography (PSG)-equivalent measures. Secondary outcomes included nocturnal CGM profiles (Ambulatory Glucose Profile, AGP), laboratory markers (HbA1c, liver enzymes), and patient-reported functional outcomes (gait, balance, tremor, daytime functioning).

AI-Augmented Clinical Reasoning Framework

The therapeutic optimization was structured as a continuous, iterative feedback loop between the patient, the supervising neurologist, and an LLM-based co-pilot (Google Gemini) used for integrative analysis and hypothesis generation (Figure 2). The neurologist maintained full clinical responsibility for all decisions. The patient curated and provided time-stamped data (medication logs, symptom diaries, diet, stressors) and digital monitoring streams (wearable, CGM). The LLM's role was to synthesize this multiplexed information, propose structured differentials for failure modes (e.g., rebound vs. absorption failure vs. glycemic triggers), and generate testable, stepwise adjustments. All LLM outputs were treated as provisional reasoning aids and were implemented only after clinician validation and safety review.

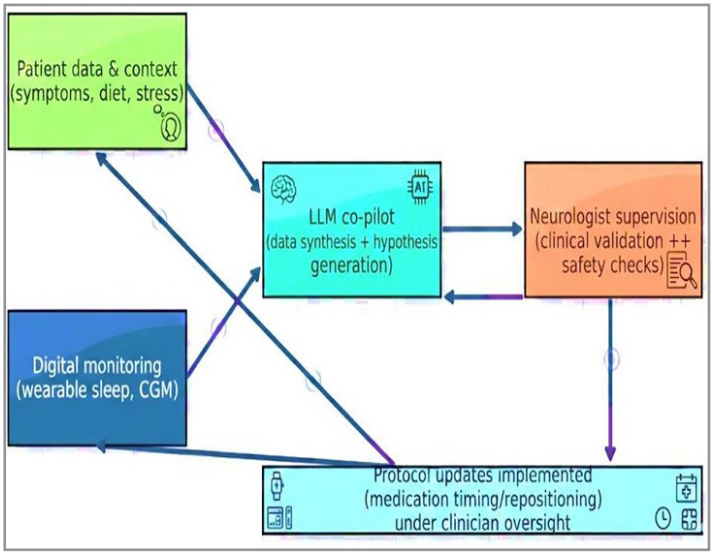

Figure 2: Human–AI Clinical Reasoning Loop (Conceptual).

Patient data, contextual factors, and digital monitoring data are fed into an LLM co-pilot for synthesis and hypothesis generation. The output is reviewed, validated, and checked for safety by a neurologist. Approved protocol updates are then implemented under clinician oversight, with the results feeding back into the system to close the loop.

Therapeutic Interventions and Rationale

Faced with the systematic failure of standard protocols, a paradigm shift was necessary, moving from a symptomatic approach to a mechanistic strategy founded on three pillars:

1. targeted molecular selection,
2. rigorous chronopharmacology,
3. strategic management of pharmacological synergies.

Table 2: The key interventions and their rationale are summarized in

Date	Major Change	Rationale
September 2025 (Baseline)	Severe insomnia, RLS, RBD. Evening levodopa use.	Suspected dopaminergic rebound/augmentation; sleep fragmentation; metabolic triggers.
Early October 2025	Replace rotigotine patch with oral pramipexole 0.18 mg (evening).	Achieve nocturnal dopaminergic stabilization with a lower augmentation risk profile than levodopa.
Oct-Nov 2025	Introduce vortioxetine (daytime).	Address affective components with a multimodal antidepressant known for minimal sleep interference.

December 5, 2025	Eliminate evening levodopa.	Crucial step to remove the primary driver of nocturnal rebound and augmentation.
December 28, 2025	Implement "gastric-sparing" chronopharmacology.	Administer evening neurological drugs on an empty stomach before dinner to maximize absorption and bypass delayed gastric emptying.
January 21, 2026	Reduce evening pregabalin from 150 mg to 125 mg.	Assess minimum effective dose to maintain RLS control while reducing next-day sedation.
February 2026	Protocol consolidation and monitoring.	Protocol consolidation and monitoring.

The chronopharmacological reorganization was critical. Activating medications like amantadine were confined to the morning and early afternoon (no later than 15:00) to prevent central nervous system stimulation at night. The evening neurological medications were administered in a "gastric-sparing" window at 19:45, on a strictly empty stomach, with dinner postponed by approximately 60-90 minutes. This strategy was designed to ensure rapid and predictable absorption, bypassing the gastroparesis associated with both PD and tirzepatide therapy (Figure 3).

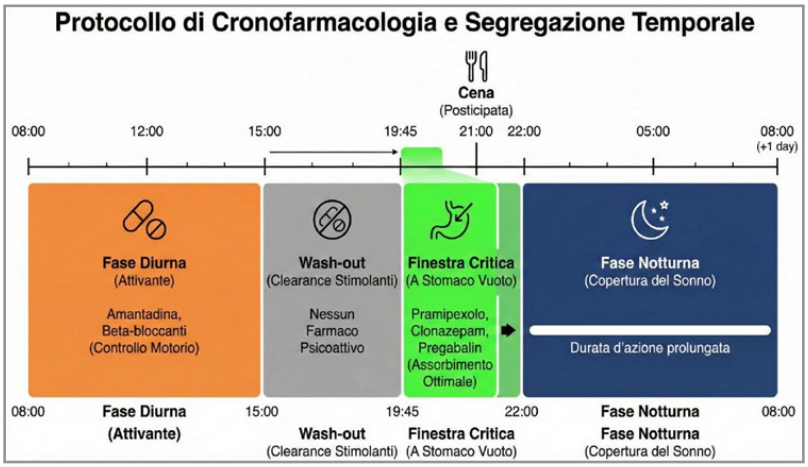

Figure 3: Optimized Chronopharmacology Protocol

The therapeutic regimen is structured to segregate activating agents (Day Phase) from sedative agents (Night Phase). A "Wash-out" period clears stimulants before the "Critical Window" for evening medication intake on an empty stomach (19:45) to ensure optimal absorption and synchronize peak drug concentration with sleep onset. The evening regimen was built on a triple-action molecular synergy.

Low-dose pramipexole (0.18 mg) provided a stable dopaminergic foundation for RLS control without the rebound of levodopa. Pregabalin (125 mg) modulated neuronal hyperexcitability by binding to α2-δ subunits of voltage-gated calcium channels. Clonazepam (~1.0 mg) was specifically targeted to suppress RBD motor activity and facilitate sleep maintenance by potentiating GABA-A receptor inhibition (Figure 4). The final optimized medication schedule is detailed in Table 3.

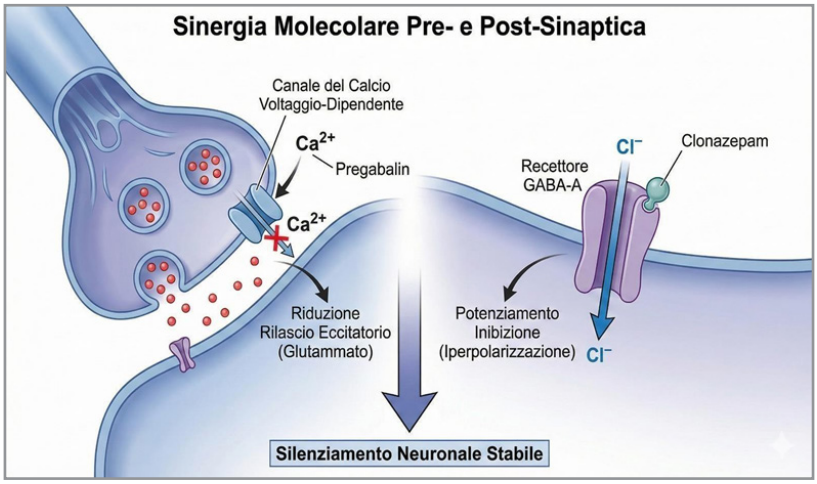

Figure 4: Pre- and Post-Synaptic Molecular Synergy for Neuronal Silencing

This mechanism illustrates the combined action of the evening medications. Pregabalin acts pre-synaptically to reduce the release of excitatory neurotransmitters (e.g., glutamate) by blocking voltage-gated calcium channels. Clonazepam acts post-synaptically to enhance the inhibitory effect of GABA at the GABA-A receptor.

Table 3: The net effect is a stable neuronal silencing conducive to sleep onset and maintenance

Time	Drug	Dose	Notes
08:00	Amantadine	100 mg	Daytime activating effect; avoid in the evening.
08:00	Propranolol	40 mg	Tremor control.
15:00	Amantadine + Propranolol	100 mg + 40 mg	Second dose within cut-off time to prevent insomnia.
19:45 (empty stomach)	Pramipexole	0.18 mg	Nocturnal dopamine stabilization for RLS.
19:45 (empty stomach)	Pregabalin	125 mg	Baseline therapy for RLS.
19:45 (empty stomach)	Clonazepam (drops)	~1.0 mg	Targeted for RBD control; titrated for efficacy vs. hangover.
19:45 (empty stomach)	Melatonin RP	2 mg	Circadian synchronization.
22:00	Non-neurological therapies	As prescribed	Administered after the critical absorption window for neurological drugs.

Results

Sleep Architecture and Continuity

The implementation of the precision protocol led to a dramatic and sustained improvement in sleep quality and duration. Monthly means for wearable-derived sleep metrics showed a marked increase following the discontinuation of evening levodopa and the implementation of the chronopharmacological strategy in December 2025. As shown in Table 4 and Figure 5, average deep sleep duration increased from a baseline of 5-8 minutes per night to 42 minutes, and REM sleep increased from 7-10 minutes to 45 minutes by February 2026.

Table 4: Total sleep time correspondingly increased from an average of under 2 hours to over 4.5 hours

Month	Average Sleep Duration (h:mm)	Deep Sleep (min)	Deep Sleep (%)	REM Sleep (min)	REM Sleep (%)
September 2025	1:48	7	7%	7	6%
October 2025	1:44	5	5%	9	9%
November 2025	2:16	8	6%	10	7%
December 2025	3:52	30	13%	23	10%
January 2026	5:08	43	14%	50	16%
February 2026	4:42	42	17%	45	18%

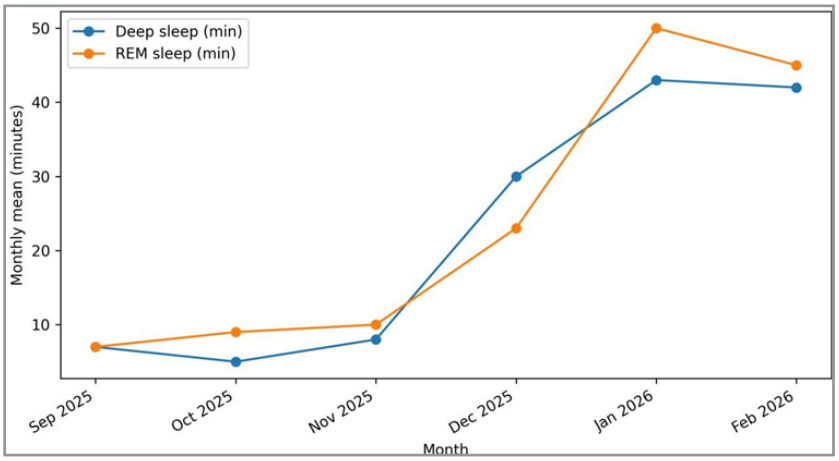

Figure 5: Monthly Mean Minutes of Wearable-Derived Deep and REM Sleep

The chart shows a clear inflection point in December 2025, corresponding to the elimination of evening levodopa and chronopharmacological reorganization, with sustained improvements in both deep and REM sleep in the subsequent months.

Metabolic and Systemic Outcomes

Metabolic improvements occurred in parallel with sleep stabilization. The resolution of NES and the restoration of a physiological circadian rhythm contributed to a reduction in HbA1c from 7.2% to 6.8% and a normalization of liver enzymes (ALT/GPT from 61 to 34 U/L) over a 12-month period. The patient also experienced a weight loss of approximately 3 kg, with body weight falling below 100 kg. CGM data revealed a crucial link between nocturnal glycemic stability and sleep quality. Nights with high glycemic variability and hyperglycemic spikes were associated with fragmented sleep, whereas stable nocturnal glucose in the 85–110 mg/dL range was associated with consolidated sleep architecture (Figure 6). This supported the hypothesis that metabolic dysregulation was a significant trigger for nocturnal arousals.

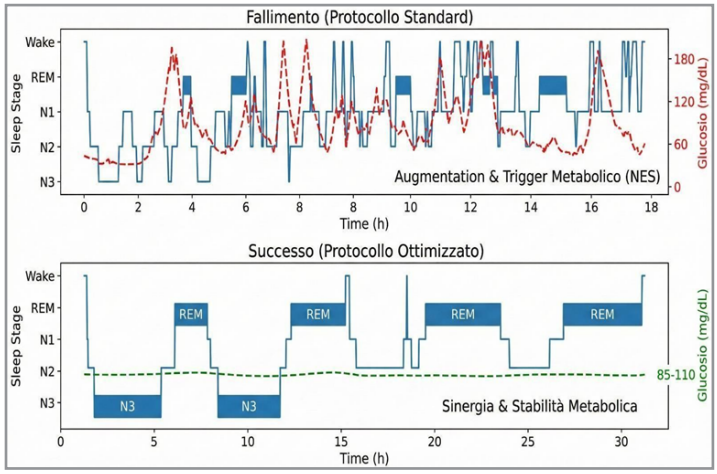

Figure 6: Comparative Analysis of Sleep Architecture and Metabolic Stability

The top panel ("Failure") shows a night with fragmented sleep architecture (frequent arousals, minimal deep/REM sleep) and high glycemic variability (red line). The bottom panel ("Success") shows a night under the optimized protocol, characterized by consolidated sleep cycles with robust deep (N3) and REM stages, and stable nocturnal glycemia (green line).

Functional Outcomes and Quality of Life

The patient reported clinically meaningful daytime improvements, including more stable gait, better balance, reduced nocturnal hyperarousal, and improved overall daytime functioning. Furthermore, the stabilization of sleep architecture and the introduction of vortioxetine coincided with a significant remission of neuropsychiatric symptoms, particularly a drastic reduction in behaviors related to Impulse Control Disorders (ICD), such as compulsive shopping. The patient also reported a marked recovery of executive functions, evidenced by a restored capacity for sustained attention and increased frustration tolerance. These self-reported outcomes, while requiring objective quantification in future work, suggest a functional reactivation of prefrontal cortical circuits previously impaired by sleep fragmentation and dopaminergic dysregulation.

Discussion

This N-of-1 case study demonstrates that a multi-modal, data-driven precision strategy can successfully resolve severe, pharmacoresistant sleep disorders in a complex patient with PARK2 PD. The success did not stem from a novel molecule but from a strategic redesign of the therapeutic regimen based on the patient's individual biology, pharmacokinetics, and real-time digital monitoring data. The first critical insight was the identification of evening levodopa as a primary iatrogenic agent driving the vicious cycle of RLS augmentation and rebound [5]. Its elimination was the cornerstone of the intervention, "cleaning" the nocturnal biochemical environment and increasing the brain's receptivity to sedative medications. This confirms that in PD patients with comorbid RLS, dopaminergic therapy must be carefully timed and balanced to avoid paradoxical effects on sleep. The second key element was the implementation of a rigorous chronopharmacological protocol. The "gastric-sparing" empty-stomach window was essential to overcome the delayed gastric emptying caused by both PD-related dysautonomia and tirzepatide therapy [10].

This highlights that medication timing and management of food-drug interactions can be as impactful as the choice of molecule itself, especially in polymedicated patients with metabolic comorbidities. Third, the approach was guided by pharmacogenetics, which explained the patient's paradoxical response to standard benzodiazepines and steered therapy towards more predictable options [11]. The final evening combination of low-dose pramipexole, pregabalin, and clonazepam created a powerful molecular synergy, addressing the distinct pathophysiological mechanisms of RLS (dopaminergic deficit, neuronal hyperexcitability) and RBD (REM atonia failure) simultaneously [3, 6, 8]. This strategy aligns with recent clinical guidelines that advocate for gabapentinoids as a first-line therapy for RLS to mitigate the long-term risk of augmentation associated with dopaminergic agents [7-14].

Finally, this work provides a real-world proof-of-concept for AI-augmented clinical reasoning. The LLM co-pilot enabled the rapid synthesis of heterogeneous data streams (pharmacogenetics, CGM, wearables, clinical notes) and the systematic exploration of interaction hypotheses that had previously been addressed in a fragmented manner. This approach preserved full

clinician authority while leveraging AI's capacity for pattern recognition and complex data integration, representing a pragmatic model for human-AI collaboration in personalized medicine.

Limitations

This study has several limitations. As an N-of-1 case report, the findings lack generalizability and are subject to potential confounders (e.g., stress, diet). The therapeutic optimization involved multiple simultaneous interventions, making it impossible to isolate the causal contribution of each component. The use of consumer wearable devices for sleep staging, while useful for intra-individual trend analysis, is not equivalent to the gold standard of PSG. Future studies should incorporate standardized pre/post assessment scales (e.g., ISI, IRLS, PDSS-2, UPDRS) and validated clinical actigraphy or PSG. AI-specific limitations include dependence on prompt framing and the risk of generating plausible but incorrect suggestions, underscoring the absolute necessity of expert clinical supervision and validation.

Conclusion

This case report illustrates a successful, AI-augmented precision medicine approach to managing complex, pharmacoresistant non-motor symptoms in a patient with PARK2 Parkinson's disease. By integrating pharmacogenetics, chronopharmacology, synergistic polypharmacy, and continuous digital monitoring, we achieved a sustained resolution of severe insomnia, RLS, and RBD, leading to significant improvements in metabolic health and quality of life. This N-of-1 study provides a pragmatic framework for leveraging AI as a cognitive co-pilot to navigate clinical complexity and personalize therapy, shifting the paradigm from symptom management to the correction of underlying pathophysiological mechanisms.

Ethics

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability

De-identified raw wearable/CGM data and a summarized AI-assisted decision-log are available upon reasonable request, subject to privacy constraints.

AI Disclosure

A commercially available LLM (Google Gemini; cloud-hosted, accessed during Oct 2025–Feb 2026) was used as a decision-support co-pilot for data synthesis and hypothesis generation. No protected health information was intentionally shared beyond what is included in this de-identified report.

References

1. Kitada, T., Asakawa, S., Hattori, N. (1998). Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature, 392(6676), 605–608. https://doi.org/10.1038/33416
2. Ratti, P. L., Joubert, S., Pereira, B. (2015). Self-reported sleep dysfunction and insomnia symptoms in Parkinson's disease: The French CoPark cohort. Parkinsonism & Related Disorders, 21(11), 1323–1329. https://doi.org/10.1016/j.parkreldis.2015.09.025
3. Alatriste-Booth, V., Rodríguez-Violante, M., Camacho-Ordoñez, A., & Cervantes-Arriaga, A. (2015). Prevalence and correlates of sleep disorders in Parkinson's disease: A polysomnographic study. Arquivos de Neuro-Psiquiatria, 73(3), 241–245. https://doi.org/10.1590/0004-282X20140228
4. Trenkwalder, C., Allen, R., Högl, B., Paulus, W., & Winkelman, J. W. (2016). Restless legs syndrome associated with major diseases: A systematic review and new concept. Neurology, 86(14), 1336–1343. https://doi.org/10.1212/WNL.0000000000002542
5. Allen, R. P., Earley, C. J. (1996). Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep, 19(3), 205–213. https://doi.org/10.1093/sleep/19.3.205
6. Allen, R. P., Chen, C., Soaita, A., et al. (2014). Comparison of pregabalin with pramipexole for restless legs syndrome. New England Journal of Medicine, 370(7), 621–631. https://doi.org/10.1056/NEJMoa1303646
7. American Academy of Sleep Medicine. (2024). Treatment of restless legs syndrome and periodic limb movement disorder: An AASM clinical practice guideline. Journal of Clinical Sleep Medicine. https://doi.org/10.5664/jcsm.11390
8. American Academy of Sleep Medicine. (2023). Management of REM sleep behavior disorder: An AASM clinical practice guideline. Journal of Clinical Sleep Medicine, 19(4), 759–768. https://doi.org/10.5664/jcsm.10424
9. Battelino, T., Danne, T., Bergenstal, R. M. (2019). Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range. Diabetes Care, 42(8), 1593–1603. https://doi.org/10.2337/dci19-0028
10. Urva, S., Quinlan, T., Landry, J., et al. (2020). The novel dual GIP and GLP-1 receptor agonist tirzepatide transiently delays gastric emptying in type 2 diabetes patients. Diabetes, Obesity and Metabolism, 22(10), 1886–1891. https://doi.org/10.1111/dom.14110
11. Inomata, S., Nagashima, A., Itagaki, F. (2005). CYP2C19 genotype affects diazepam pharmacokinetics and emergence from general anesthesia. Clinical Pharmacology & Therapeutics, 78(6), 647–655. https://doi.org/10.1016/j.clpt.2005.08.020
12. Birrer, V. (2024). Evaluating reliability in wearable devices for sleep staging. npj Digital Medicine. https://doi.org/10.1038/s41746-024-01016-9
13. Lee, T., Cho, Y. (2023). Accuracy of 11 wearable, nearable, and airable consumer sleep trackers: A prospective multicenter validation study. JMIR mHealth and uHealth, 11, e50983. https://doi.org/10.2196/50983
14. Winkelman, J. W., Wipper, B. (2026). Restless legs syndrome: A review. JAMA. https://doi.org/10.1001/jama.2025.23247