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Review

When Dopamine Never Sleeps: Chronopharmacologic Insights into Continuous 24-Hour Infusion Therapy

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ABSTRACT

Background: Dopamine plays a pivotal role not only in motor control but also in the regulation of circadian rhythms and sleep–wake architecture. Continuous dopaminergic stimulation (CDS), achieved through 24-hour levodopa/carbidopa infusion, provides stable dopaminergic tone in advanced Parkinson's disease (PD). While this strategy improves motor fluctuations, its influence on diurnal dopamine physiology and circadian homeostasis remains poorly understood.

Objective: This review critically examines how 24-hour dopaminergic infusion may interact with endogenous dopamine rhythms, clock gene expression, and sleep–REM physiology, areas largely underexplored in current literature.

Methods: A comprehensive PubMed search was conducted through February 2025 using terms related to "dopamine," "circadian rhythm," "continuous dopaminergic stimulation," and "sleep architecture." Animal and human studies addressing dopaminergic circadian modulation or infusion therapies were synthesized.

Results: Evidence suggests that CDS may flatten physiological dopamine oscillations, induce receptor desensitization, and influence REM/NREM regulation and peripheral clock gene activity. Preliminary clinical findings indicate improved subjective sleep quality but uncertain effects on circadian entrainment.

Conclusion: Continuous 24-hour dopaminergic infusion represents a major therapeutic advance in PD. However, its chronopharmacologic effects on circadian signaling and sleep structure warrant systematic investigation through polysomnography and molecular chronobiology to optimize both motor and non-motor outcomes.

Keywords: Continuous Dopaminergic Stimulation (CDS), Foslevodopa/Foscarbidopa, Circadian Dopamine Rhythms, Parkinson's Disease

INTRODUCTION

Dopamine (DA) is a central neurotransmitter in motor control, reward pathways, and increasingly recognized as a modulator of sleep–wake behaviour and circadian regulation. In healthy physiology, dopaminergic neurons (notably in the substantia nigra, ventral tegmental area) display tonic and phasic firing, and downstream DA receptor occupancy and metabolism show diurnal-oscillatory patterns.

In disorders such as Parkinson's disease (PD), these rhythms become disturbed, contributing to motor fluctuations and sleep/circadian dysfunction. Given the development of continuous dopaminergic

delivery (e.g., 24-h infusion of levodopa or other analogues) in advanced PD, the chronobiologic implications of continuous dopaminergic stimulation (CDS) merit consideration. While many studies focus on motor outcomes of CDS, less attention has been given to how continuous DA supply may interact with circadian physiology, sleep architecture (including REM/NREM cycling), and molecular clock systems.[1-2]

Recent formulation advances have extended dopaminergic replacement beyond oral and intestinal gel therapies to include fully continuous, subcutaneous infusion systems. In 2024, the U.S. Food and Drug Administration approved foslevodopa/foscarbidopa (Vyalev™), a soluble prodrug combination of levodopa and carbidopa designed for 24-hour subcutaneous delivery. These prodrugs are rapidly hydrolyzed by systemic esterases to release active levodopa and carbidopa, maintaining stable plasma levodopa levels comparable to intrajejunal levodopa–carbidopa intestinal gel but with less invasive administration.[3] Continuous infusion reduces plasma fluctuations, dyskinesia risk, and "off" periods in advanced Parkinson's disease. However, its chronopharmacologic implications—including potential effects on circadian dopamine oscillations, sleep–wake architecture, and REM behavior—remain largely unexamined. This review evaluates the background of DA's circadian biology, the evidence for continuous infusion therapies, and elaborates mechanistic hypotheses and research directions on how 24-hour infusion might alter diurnal DA physiology and sleep/REM behaviour.

METHODS OF LITERATURE REVIEW

We performed a comprehensive search in PubMed (via NCBI) up to June 2025 using search terms: "dopamine AND circadian", "levodopa infusion AND sleep Parkinson", "continuous dopaminergic stimulation AND sleep architecture", "dopaminergic infusion 24-hour Parkinson's sleep", and "clock genes dopamine regulation". We included peer-reviewed English-language original research, reviews and clinical studies addressing (i) circadian dopamine physiology, (ii) continuous or extended dopaminergic infusion therapies in PD or animal models, and (iii) sleep/circadian outcomes. Abstracts were reviewed, full text assessed when available, and we selected 15 key articles with PubMed identifiers. Our emphasis is on mechanistic chronopharmacology rather than motor-only outcomes.

Diurnal Dopamine Physiology and Circadian Modulation

Dopamine rhythms and clock gene interactions

Evidence indicates that components of the circadian clock are intimately linked with dopaminergic systems. For instance, the molecular clock machinery in the striatum can regulate tyrosine hydroxylase (TH) expression, dopamine transporter expression and DA turnover, and reciprocally DA signalling can modulate local clock gene expression (e.g., Per1/2, Bmal1). In animal work, TH mRNA and protein levels in midbrain dopaminergic nuclei double between light and dark phases; disruption of serotonin pathways blunted these rhythms, suggesting upstream modulators. Circadian clock gene mutants (e.g., Clock knock-out mice) show enhanced dopaminergic firing and altered reward and activity rhythms.[4,5] Therefore, dopaminergic tone is not static but embedded within a 24-h oscillatory framework, implicating DA in both central and peripheral time-keeping.

Dopamine, sleep architecture and REM behaviour

DA influences arousal, sleep-wake transitions, NREM/REM gating and is implicated in REM sleep behaviour disorder (RBD). Sleep deprivation in humans reduces D2/D3 receptor availability in ventral striatum.[6] Animal studies show that dopamine release increases during REM episodes in some areas, and pharmacologic blockade of D2 receptors alters REM latency or REM duration. In PD, disruptions of dopaminergic neurons are associated with sleep fragmentation, excessive daytime sleepiness, nocturnal

akinesia, and RBD.[7]

Therefore, the normal diurnal patterns of dopamine may support stable sleep architecture; conversely, disruption of those patterns may underlie sleep-/REM-related non-motor symptoms.

Implications of pulsatile vs continuous dopaminergic stimulation

Traditional oral levodopa therapy leads to high peaks and low troughs of plasma/brain levodopa, contributing to motor fluctuations and dyskinesia via receptor sensitization and "pulsatile" DA receptor stimulation. Continuous infusion therapies (e.g., intrajejunal levodopa–carbidopa gel) produce smoother pharmacokinetics, fewer off-periods and reduced dyskinesia in many studies.[8] From a chronopharmacologic perspective, the key question becomes: how does sustained, constant dopaminergic stimulation interact with normal diurnal dopamine fluctuations? Does continuous infusion simply override the oscillation (flattening amplitude) or does it integrate with endogenous rhythms to restore more physiological signalling?

24-Hour Dopaminergic Infusion: Evidence and Sleep-Circadian Outcomes

Evidence of continuous infusion in advanced PD

Continuous delivery systems—notably intrajejunal levodopa–carbidopa intestinal gel (LCIG) or emerging subcutaneous 24h infusions—have shown efficacy in reducing off-time, increasing on-time, and improving quality of life in advanced PD patients.[9]

For instance, a study of intrajejunal infusion over 18 months in advanced PD reported sustained improvement in motor fluctuations and non-motor symptoms.[10]

Emerging work on subcutaneous 24-h infusion (e.g., ND0612 or subcutaneous levodopa/carbidopa) shows promising ON-time gains and novel device approaches.

Sleep and nocturnal motor outcomes with infusion

Most sleep data in infusion literature are derived from patient-reported sleep scales rather than full polysomnography. For example, a longitudinal study of LCIG infusion found improvements in the Pittsburgh Sleep Quality Index (PSQI) and Parkinson's Disease Sleep Scale (PDSS-2) at 6 and 12 months.[11]

A review of 24-hour LCIG infusion noted improved night-time akinesia, freezing of gait, dyskinesia, and sleep quality.[8] However, objective sleep architecture (REM latency, RSWA, sleep-stage distributions) in the context of 24-h dopaminergic infusion remains under-reported. A recent review on non-oral dopaminergic continuous delivery listed sleep dysfunction as a major non-motor target but noted a paucity of PSG studies.[12]

Figure 1: Dopamine oscillations (normal vs continuous infusion)

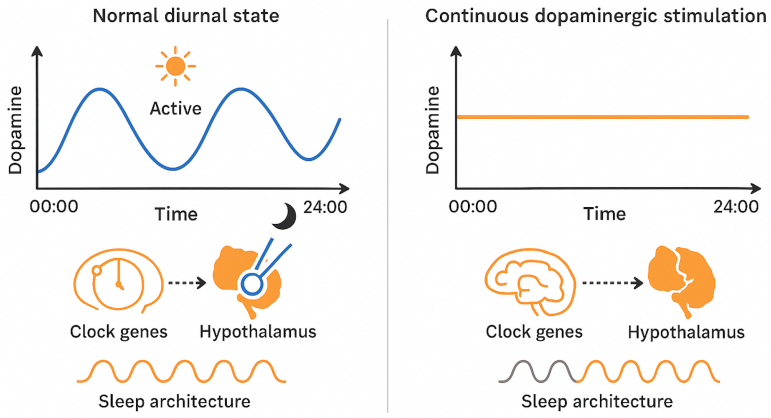

Figure 1 illustrates how 24-hour continuous dopaminergic infusion modifies endogenous diurnal dopamine signaling and downstream physiological rhythms. In the normal diurnal state (left panel),

dopamine levels fluctuate cyclically, peaking during the active/wake phase and declining during sleep, maintaining alignment with circadian clock genes and sleep architecture (including REM–NREM cycling). Under continuous dopaminergic stimulation (right panel), plasma and extracellular dopamine levels remain stable, reducing pulsatility and potentially blunting natural circadian oscillations.

Chronopharmacologic hypotheses of infusion impact

Given the above, the following mechanistic hypotheses arise for how 24-hour infusion might alter circadian DA physiology, sleep architecture and REM behaviour:

Flattening of amplitude of diurnal DA fluctuations

Continuous infusion reduces the normal peaks and troughs of brain/plasma levodopa/DA, thus diminishes amplitude of DA oscillations. This may reduce pathological variability (good for motor fluctuations) but may also diminish low-DA troughs that may be important for sleep initiation or deep sleep phases.

Receptor adaptation and sensitivity changes

Constant dopaminergic tone may induce receptor down-regulation, altered D1/D2 receptor sensitivity, or changes in downstream signalling. This might impact sleep–wake regulation (e.g., increased baseline arousal) or REM gating.

Clock gene entrainment in dopaminoceptive circuits

Dopamine modulates local clock gene expression in striatum and other brain regions. Continuous DA may shift or damp local clock gene rhythms (e.g., PER2) and thus alter local circadian outputs independent of the suprachiasmatic nucleus (SCN).

Sleep-architecture effects

By reducing nocturnal motor issues (akinesia, rigidity), continuous infusion may improve sleep continuity and reduce arousals. On the flip side, elevated dopaminergic tone at night may interfere with slow-wave sleep (SWS) depth or REM onset, potentially altering memory consolidation or restorative processes.

Peripheral/cardiometabolic circadian consequences

Dopaminergic input to SCN and peripheral tissues influences autonomic and metabolic rhythms. Continuous infusion might attenuate normal night-time sympathetic dips or alter heart rate variability, blood pressure dipping, glucose/insulin rhythms, potentially impacting cardiovascular/metabolic risk in PD patients.[13-15]

DISCUSSION

Continuous subcutaneous foslevodopa/foscarbidopa infusion represents a new frontier in dopaminergic chronopharmacology. By providing uninterrupted dopaminergic stimulation over 24 hours, it effectively mitigates motor fluctuations but may reshape the physiological diurnal rhythm of dopamine signaling. Endogenous dopamine release normally exhibits circadian oscillations, peaking during wakefulness and declining during sleep, which are crucial for motor vigor, attention, and REM regulation. Persistent dopaminergic tone could attenuate these natural oscillations, potentially influencing sleep architecture, REM behavior, and circadian gene expression in striatal and hypothalamic circuits. Preliminary clinical observations suggest that 24-hour infusion may improve nocturnal akinesia and sleep continuity, yet systematic evaluation of polysomnographic and chronobiologic parameters remains absent. Future studies should incorporate melatonin profiling, actigraphy, and molecular clock biomarkers to elucidate whether long-term continuous stimulation entrains, blunts, or reconfigures dopamine-dependent

circadian networks. Understanding these effects may guide individualized dosing schedules aligned with chronobiological principles.[16-18]

Practical Clinical Implications

For advanced PD patients with marked nocturnal motor issues (akinesia, freezing, nocturia), 24-h infusion may provide improved overnight motor stability and subjective sleep quality.

Clinicians should be aware of potential sleep/circadian side-effects: infusion at nighttime may raise dopaminergic tone when physiologic dip usually occurs—monitor for insomnia, reduced SWS, altered REM latency, or altered daytime alertness.

Infusion regimens could be individualized: e.g., slightly reduced rate overnight to allow a mild dip in DA tone and perhaps better sleep architecture, or higher rate overnight in patients with severe RBD or nocturnal freezing.

Consider complementary assessments: sleep questionnaires (PSQI, PDSS-2) plus actigraphy or PSG when feasible, and autonomic/metabolic monitoring (HRV, nocturnal BP dipping), especially in patients with cardiovascular/metabolic comorbidities.

CONCLUSION

Continuous 24-hour dopaminergic infusion represents a major therapeutic advance for advanced PD. While the focus has rightly been on motor stabilization, its chronopharmacologic consequences for circadian dopamine physiology, sleep architecture, and REM behaviour are underexplored. Dopamine does not operate in a vacuum — it is embedded in the brain's clocks, sleep networks, and metabolic rhythms. Continuous infusion may beneficially smooth pathological fluctuations, but it may also alter endogenous rhythm amplitude or phase in ways that affect sleep quality, REM integrity, and peripheral physiological rhythms. Recognizing and investigating these chronobiologic effects will allow clinicians and researchers to optimize therapy for both motor and non-motor domains of PD. Future research should integrate motor, sleep, chronobiologic, and metabolic endpoints to illuminate the full impact of continuous dopaminergic therapies.

Abbreviations

CDS – Continuous Dopaminergic Stimulation; CNS – Central Nervous System; CSF – Cerebrospinal Fluid; DA – Dopamine; DCI – Dopamine Conversion Inhibitor (carbidopa/benserazide); D1R / D2R – Dopamine D1 Receptor / Dopamine D2 Receptor; DBS – Deep Brain Stimulation; FDA – Food and Drug Administration; FOC/FSC – Foslevodopa/Foscarbidopa (prodrug formulation); GI – Gastrointestinal; HPA Axis – Hypothalamic–Pituitary–Adrenal Axis; LCIG – Levodopa–Carbidopa Intestinal Gel; LD – Levodopa; LID – Levodopa-Induced Dyskinesia; MTNR1A/B – Melatonin Receptor 1A / 1B; NREM – Non–Rapid Eye Movement Sleep; PD – Parkinson's Disease; PK – Pharmacokinetics; PL – Pulsatile Levodopa (oral dosing); REM – Rapid Eye Movement Sleep; RLS – Restless Legs Syndrome; SC – Subcutaneous; SC-FOS/SC-FOSCAR – Subcutaneous Foslevodopa/Foscarbidopa infusion; SCN – Suprachiasmatic Nucleus; UPDRS – Unified Parkinson's Disease Rating Scale; UVL – Ultraviolet Light (for circadian entrainment studies); VMT2 – Vesicular Monoamine Transporter-2; ZT – Zeitgeber Time (circadian reference timing). PSQI – Pittsburgh Sleep Quality Index; PDSS-2 – Parkinson's Disease Sleep Scale – Version 2; PSG — Polysomnography.

Conflict of Interest

The authors declare no conflicts of interest relevant to this article.

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