Timing of Dopaminergic Medication Relative to Physiotherapy Delivery in Adults with Parkinson's Disease: A Scoping Review

Running title: *Medication Timing and Physiotherapy in PD*

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Abstract

Background.

Levodopa pharmacotherapy in Parkinson's disease (PD) produces cyclic variation in motor function through alternating ON and OFF medication states. Physiotherapy is recommended across all disease stages, yet whether sessions are scheduled during ON or OFF states, or at specific post-dose intervals, may influence both therapeutic benefit and safety. The extent to which the timing of dopaminergic medication relative to physiotherapy has been reported, implemented, or evaluated in clinical research has not been comprehensively evaluated.

Objective.

To map and synthesise the available evidence on the scheduling of dopaminergic medications relative to physiotherapy and exercise interventions in adults with Parkinson's disease, and to identify evidence gaps that warrant further investigation.

Eligibility criteria.

Studies of any design enrolling adults with idiopathic PD that reported either the medication state (ON/OFF) during physiotherapy assessment or the post-dose interval at which exercise was conducted.

Information sources.

Thirteen electronic databases were searched from inception to 15 February 2026: PubMed/MEDLINE, Embase, Scopus, Web of Science, CINAHL, PEDro, SPORTDiscus, Cochrane Library, Epistemonikos, PROSPERO, Open Science Framework, INPLASY, and Google Scholar.

Methods.

The review was conducted in accordance with the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis for scoping reviews and reported using the PRISMA Extension for Scoping Reviews (PRISMA-ScR). Evidence was synthesised narratively with descriptive analysis, evidence mapping, and thematic synthesis. No meta-analysis was conducted.

Results.

Twenty-eight sources were included: seven systematic reviews or meta-analyses, six registered protocols, nine primary clinical or pharmacokinetic studies, and six additional sources identified through citation searching (1992–2025). Physical exercise did not significantly alter systemic levodopa pharmacokinetics (AUC, Cmax) in most participants across three crossover pharmacokinetic studies. Motor pharmacodynamic responses, however, differed by disease stage and time post-dose. Biomechanical gait parameters were significantly superior in the ON state compared with a standardised OFF state. One study observed improved motor response at 120–150 minutes post-dose on exercise days in moderate-stage patients; a second observed significant motor deterioration at 180 minutes in advanced patients. No study systematically evaluated physiotherapy outcomes at standardised sequential post-dose intervals within the same participant cohort. Critical evidence gaps were identified in relation to drug formulation, disease stage, biological sex, and reporting standards.

Conclusions.

Evidence on the scheduling of dopaminergic medication relative to physiotherapy in PD is limited in scope and methodologically inconsistent. Available data suggest that medication state influences motor capacity during rehabilitation, but the evidence does not yet support precise scheduling recommendations. Standardised reporting of medication timing and state verification is a prerequisite for future synthesis.

Keywords: *Parkinson's disease; levodopa; dopaminergic medication; physiotherapy; exercise; medication timing; ON state; OFF state; motor fluctuations; scoping review*

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Introduction

Parkinson's disease is the second most prevalent neurodegenerative condition globally, with an estimated 7–10 million people affected worldwide and a growing incidence associated with population ageing.1 The condition arises from progressive dopaminergic neurodegeneration within the substantia nigra pars compacta, producing the cardinal motor features of bradykinesia, rigidity, resting tremor, and postural instability.2 A broad spectrum of non-motor manifestations — including cognitive impairment, autonomic dysfunction, and sleep disruption — compounds functional decline and reduces quality of life.3

Levodopa, in combination with a peripheral dopa-decarboxylase inhibitor, remains the most effective pharmacological treatment for PD motor symptoms.4 With sustained treatment, however, a large proportion of patients develop motor fluctuations — estimated to affect approximately 30% of patients at five years and more than 80% at ten years.5 These arise from progressive loss of striatal dopaminergic buffering capacity, rendering the motor response increasingly sensitive to oscillating plasma drug concentrations. The resulting alternating states — ON, characterised by adequate symptom control, and OFF, characterised by re-emergence of motor disability — create the pharmacodynamic context within which all physical rehabilitation is delivered.

Physiotherapy (PT) is recommended across all disease stages in major PD guidelines, with evidence supporting benefits from a range of modalities including gait training, balance rehabilitation, resistance exercise, aerobic conditioning, cueing strategies, and task-specific training.6 Several systematic reviews and meta-analyses have strengthened this evidence base. Okada et al. reported that long-term physiotherapy (≥6 months) significantly reduced motor severity assessed in the OFF medication state (standardised mean difference [SMD] −0.65, p = 0.001) and reduced levodopa-equivalent dose (LED; SMD −0.49, p = 0.02) in a pooled analysis of ten randomised controlled trials.7 Bloem and colleagues established Level 1 evidence for aerobic exercise improving cardiorespiratory fitness in PD.8

Despite these advances, a question with direct practical implications has received comparatively limited systematic attention: how has the timing of dopaminergic medication relative to physiotherapy sessions been reported, implemented, and evaluated in PD research? The ON and OFF states differ substantially in their neurobiological substrate: joint range of motion, muscle activation, motor learning capacity, fall risk, and the physiological response to exercise all vary across the pharmacodynamic cycle.9 A small number of pharmacokinetic crossover studies have addressed exercise during or shortly after levodopa absorption, with complex and partly conflicting findings. Muhlack et al. reported that moderate-intensity exercise improved the pharmacodynamic motor response at 120–150 minutes post-dose without altering plasma pharmacokinetics.10 Figura et al., using a comparable design in a more heterogeneous sample, found no pharmacokinetic changes across disease subgroups but observed significant motor deterioration at 180 minutes on exercise days specifically in advanced patients.11 These findings cannot be directly compared, and neither has been replicated in a larger independent trial.

To our knowledge, no published systematic review or scoping review has addressed the scheduling of dopaminergic medications relative to physiotherapy as its primary objective. Several reviews acknowledge medication state as a methodological consideration, and a small number present outcomes separately by ON and OFF state. No review, however, systematically maps this evidence across post-dose timing intervals, medication formulations, exercise modalities, and disease stages within a unified framework. Given the heterogeneity of available studies and the breadth of the question, a scoping review — designed to map the extent and nature of available evidence rather than estimate a pooled effect — is the most appropriate methodology at this stage. This review will also determine whether the available evidence warrants and would support a future systematic review with meta-analysis.

Objectives

Primary Objective. To systematically map and synthesise the evidence on the scheduling of dopaminergic medications relative to physiotherapy and exercise interventions in adults with Parkinson's disease, including documentation of medication state (ON/OFF) or post-dose timing intervals at

which physiotherapy was conducted or outcomes were assessed.

Secondary Objectives. To identify the physiotherapy modalities studied in relation to medication state; to characterise how disease stage, biological sex, and medication formulation are reported in relation to medication timing; to describe the outcome measures used; and to identify evidence gaps warranting further research.

Review Questions

Primary Review Question

How has the timing of dopaminergic medication relative to physiotherapy interventions been reported, implemented, and evaluated in adults with Parkinson's disease?

Secondary Review Questions

1. At what post-dose intervals relative to dopaminergic medication administration has physiotherapy or exercise been delivered or assessed in included studies?
2. Which physiotherapy and exercise modalities have been studied in relation to ON/OFF medication state or specific post-dose timing intervals?
3. How do disease stage, biological sex, and medication formulation modulate the relationship between medication timing and physiotherapy outcomes, as reported in included sources?
4. What outcome measures have been used to evaluate the interaction between dopaminergic medication state and physiotherapy, and how consistently is medication state documented at the time of outcome assessment?
5. What pharmacokinetic or pharmacodynamic changes have been reported in association with exercise performed at different intervals relative to dopaminergic medication?
6. What clinical practice recommendations, if any, have been provided in the included literature regarding the scheduling of physiotherapy relative to dopaminergic medication administration?

Methods

Study Design

This scoping review was conducted in accordance with the JBI Manual for Evidence Synthesis13 and reported using the PRISMA-ScR checklist.14 The review followed the five-stage framework of Arksey and O'Malley,15 as refined by Levac, Colquhoun, and O'Brien.16 The review was not prospectively registered. Following completion of the review, the protocol and supporting materials were registered on the Open Science Framework (OSF) as an Open-Ended Registration to improve transparency and reproducibility (OSF project: https://osf.io/n2qky; DOI: 10.17605/OSF.IO/5X27W). This registration documents the completed review and should not be interpreted as a prospective preregistration.

Population, Concept, and Context Framework

Eligibility was defined using the JBI Population, Concept, and Context (PCC) framework.

Population. Adults (≥18 years) with a confirmed clinical diagnosis of idiopathic Parkinson's disease at any stage of disease severity. Atypical parkinsonian syndromes were excluded owing to their distinct pharmacological profiles and disease trajectories.

Concept. The temporal scheduling of dopaminergic medications (levodopa formulations, dopamine agonists, MAO-B inhibitors, COMT inhibitors) relative to physiotherapy or structured exercise, including specification of ON/OFF medication state, post-dose timing intervals, wearing-off, peak-dose windows, and continuous infusion therapy.

Context. Any clinical or research setting in which physiotherapy or structured exercise was delivered to adults with PD, regardless of country, healthcare system, or delivery modality (in-person, telerehabilitation, home-based).

Eligibility Criteria

Inclusion Criteria

- Adults (≥18 years) with a confirmed diagnosis of idiopathic Parkinson's disease at any H&Y stage.
- Studies reported on the temporal scheduling of dopaminergic medication relative to physiotherapy or exercise, including specification of ON/OFF medication state, post-dose timing intervals, wearing-off, peak-dose periods, or continuous infusion therapy.
- Any clinical or research setting.
- Any study design, including randomised and non-randomised controlled trials, crossover studies, prospective and retrospective cohort studies, case series (n≥5), observational studies, systematic reviews, scoping reviews, pharmacokinetic studies, registered protocols, and clinical practice guidelines.
- No restriction on publication date.
- No language restriction at identification or title/abstract screening stages; full-text review was conducted in English or with a verified translation.

Exclusion Criteria

- Atypical parkinsonian syndromes (multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies, corticobasal syndrome).
- Studies evaluating exercise or dopaminergic medication in isolation, with no reporting of temporal coordination or medication state during physiotherapy.
- Studies exclusively enrolling paediatric populations (<18 years) or animal models.
- Single case reports (n = 1).
- Conference abstracts containing insufficient methodological information for data charting.

Information Sources

The following databases were searched: PubMed/MEDLINE, Embase, Scopus, Web of Science, CINAHL, PEDro, SPORTDiscus, Cochrane Library, Epistemonikos, PROSPERO, Open Science Framework (OSF), INPLASY, and Google Scholar. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were additionally searched for ongoing or unpublished trials. All databases were searched from inception to 15 February 2026.

Search Strategy

A three-domain Boolean search strategy was developed in collaboration with a medical librarian. Domain 1 addressed the population (PD terminology); Domain 2 addressed the concept (dopaminergic medication, timing, and pharmacokinetic terms); Domain 3 addressed the context (physiotherapy and exercise terminology). MeSH terms (PubMed), Emtree terms (Embase), and free-text keywords with truncation, phrase searching, and proximity operators were applied. The complete PubMed search string is provided in Appendix A. Adapted strategies for Embase and Scopus are also appended. Forward and backward citation searching was performed for all included primary studies.

Study Selection

All records were imported into a reference management platform and deduplicated. Screening proceeded in two sequential phases. In Phase 1, two independent reviewers (F.M.P. and A.S.) assessed all records at the title and abstract level against the PCC eligibility criteria. Records were excluded only where it was unambiguous that eligibility criteria were not met. Disagreements were resolved through discussion, with adjudication by a third reviewer where necessary. In Phase 2, full-text articles for records passing Phase 1 were independently assessed by the same two reviewers using a standardised eligibility form. Reasons for exclusion at the full-text stage were documented for all records. A PRISMA-ScR flow diagram (Figure 1) was constructed to present the screening process using the actual numerical yield from each phase.

Data Charting

A standardised JBI data-charting form (Appendix C) was developed a priori and piloted on five sources before application to the full corpus. The form captured: bibliographic details and study registration; population characteristics; medication name, formulation, dose, and LED; medication timing (ON/OFF state specification, post-dose interval in minutes, method of state verification, peak-dose or wearing-off specification); physiotherapy intervention details; outcome measures and medication state at the time of assessment; main reported findings; author-identified knowledge gaps; and reviewer comments. Data were extracted by F.M.P. (second author) and independently verified by A.S. (first author). Discrepancies were resolved through consensus discussion.

Data Synthesis

Consistent with JBI guidance for scoping reviews, no meta-analysis was conducted. Evidence was synthesised through: (1) descriptive summary of source characteristics; (2) a two-dimensional evidence map plotting medication timing categories against physiotherapy intervention types (Table 5); (3) inductive thematic synthesis to identify recurring cross-cutting themes; and (4) a conceptual summary of the relationship between IR levodopa pharmacokinetics and reported physiotherapy scheduling, drawing on pharmacokinetic data from included primary studies.

Methodological Quality Appraisal

In accordance with JBI guidance for scoping reviews, formal methodological quality appraisal was not conducted as a prerequisite for inclusion or exclusion. The purpose of this review is to map the extent and nature of available evidence. Methodological limitations of individual sources were documented during data charting and reported narratively.

Protocol Registration and Ethics

This review was not prospectively registered. Following completion of the review, the protocol and supporting materials were registered on OSF as an Open-Ended Registration to enhance transparency and reproducibility (https://osf.io/n2qky; DOI: 10.17605/OSF.IO/5X27W). Ethical approval was not required, as this review synthesises published and registered literature and involves no primary data collection from human participants.

Results

Study Selection

The systematic search across 13 databases and two clinical trial registries yielded 3,248 records. An additional 18 records were identified through other sources (forward and backward citation searching of primary studies). Following removal of 303 duplicate records, 2,945 unique records were screened at the title and abstract level. Of these, 2,862 were excluded on the basis of title and abstract review. Eighty-three records proceeded to full-text assessment for eligibility, of which 55 were excluded: 20 did not enrol the correct population; 11 did not address the concept of medication timing relative to physiotherapy; eight did not report relevant outcomes; six were narrative review articles without primary data; four were conference abstracts lacking sufficient methodological information; three were registered protocols without reportable results; and three could not be retrieved in full text. Twenty-eight sources met all eligibility criteria and are included in this synthesis. The screening process is presented in Figure 1 (PRISMA-ScR flow diagram).

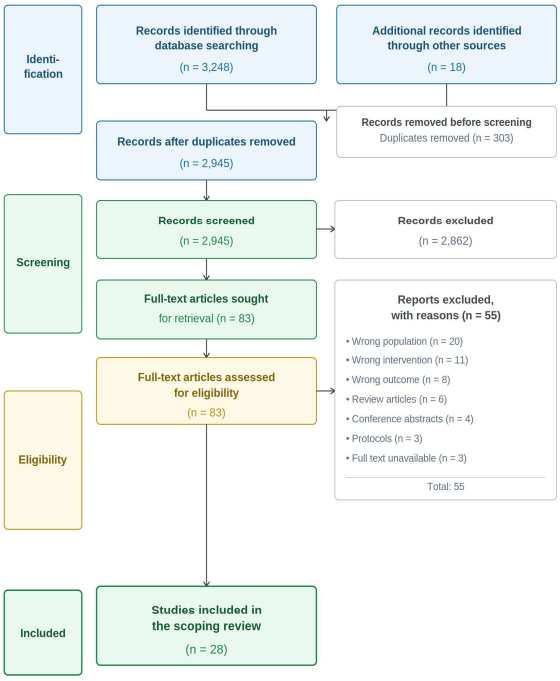

Figure 1. PRISMA 2020 flow diagram illustrating the search and selection process of eligible studies included in the scoping review. All databases were searched from inception to 15 February 2026.

Characteristics of Included Sources

The 28 included sources comprised seven systematic reviews or meta-analyses, six registered protocols (PROSPERO, OSF, and INPLASY registrations), nine primary clinical or pharmacokinetic studies, and six additional sources identified through citation searching. Studies originated from Germany (n = 3), Japan (n = 2), Italy (n = 1), the Netherlands (n = 1), the USA (n = 1), China (n = 1), and India/USA (n = 1); three registered protocols did not specify a single country of origin. Publication dates ranged from 1992 to 2025. Across the nine primary clinical or pharmacokinetic studies, sample sizes in individual studies ranged from 10 to 663 participants, with mean ages from 58.6 to 67.4 years. Disease severity spanned H&Y stages 1–4 in primary studies; H&Y 4–5 was represented only in one registered protocol. Detailed source characteristics are presented in Table 1.

Primary clinical and pharmacokinetic studies (n = 9).

Three primary studies addressed pharmacokinetic and pharmacodynamic interactions between exercise and levodopa. Figura et al. (2024) conducted a two-day randomised crossover trial in 29 participants across three predefined subgroups: levodopa-naïve patients with PD (LNPD; n = 12), advanced patients with established wearing-off (APD; n = 10), and healthy controls (n = 7). Participants received soluble levodopa/benserazide 200/50 mg; on exercise days, spinning cycle ergometry was initiated immediately post-dose. Primary endpoints included serial plasma pharmacokinetic parameters and UPDRS-III assessed at scheduled time points up to 180 minutes. Muhlack et al. (2007) used a comparable two-day crossover design in 10 participants, with cycle ergometry at aerobic threshold immediately post-dose and serial UPDRS-III assessments at 30-minute intervals. Nutt et al. (1992) randomised 10 participants to cycle ergometry versus physical rest during the absorption phase, with serial plasma levodopa sampling as the primary outcome.

Shida et al. (2024) evaluated gait biomechanics in 22 participants using 3D motion capture (44 reflective markers, 12 cameras, 150 Hz) comparing standardised ON (1 hour post-dose) and OFF (≥12-hour withdrawal) states during overground walking at self-selected speed. Contin et al. (2022) conducted a two-year multicentre prospective cohort study in 28 levodopa-naïve patients with serial pharmacokinetic sampling and standardised clinical assessment, stratified by biological sex as a pre-specified variable. Okada et al. (2021) synthesised 10 RCTs (663 participants) evaluating long-term physiotherapy versus usual care.

Systematic reviews and meta-analyses (n = 6).

Beyond Okada et al. (2021), five additional systematic reviews were included. Bloem and

Radboud UMC (2020) reviewed aerobic exercise evidence in PD, explicitly restricting motor outcome assessment to the OFF state to standardise measurement and avoid pharmacological confounding. Krieg et al. (2025) examined attentional focus strategies across ON and OFF states in nine primary studies. Li and Hu (2025) and Srinivas et al. (2024) reported exercise outcomes without specifying medication state in their syntheses. The Self-Management Review Group (2022) addressed self-management programmes without addressing temporal scheduling.

Registered protocols (n = 3).
Three registered protocols were identified: PROSPERO CRD420251022480 (scoping review of physiotherapy in advanced PD, H&Y 4–5, with ON/OFF state accepted but not as primary focus); PROSPERO CRD42020206939 (systematic review of long-term physiotherapy for motor-symptom prevention, with ON/OFF subgroup analysis planned); and OSF.IO/ZVPX5 (scoping review of telerehabilitation-based physiotherapy with no medication scheduling outcome specified).

Table 1
Characteristics of Included Sources (n = 28)

First Author (Year)	Country	Study Design	n	Mean Age (SD), Years	H&Y Stage	Dopaminergic Medication	PT Intervention and Reported Timing
Figura et al. (2024)	Germany	Two-day randomised crossover (3 subgroups)	29	60.2 (9.1)	1–3	Levodopa/benserazide 200/50 mg soluble IR tablet	Spinning cycle ergometry initiated immediately post-dose (exercise day) vs. rest day; serial plasma PK sampling and UPDRS-III
Muhlack et al. (2007)	Germany	Two-day randomised crossover	10	63.1 (7.4)	2–3	Levodopa IR; single therapeutic dose	Cycle ergometry at aerobic threshold, initiated immediately post-dose vs. rest day; serial UPDRS-III at 30-min intervals to

First Author (Year)	Country	Study Design	n	Mean Age (SD), Years	H&Y Stage	Dopaminergic Medication	PT Intervention and Reported Timing
							150 min
Nutt et al. (1992)	USA	Randomised physiological crossover	10	61.8 (8.2)	2–4	Standard oral levodopa	Cycle ergometry during absorption vs. physical rest; serial plasma levodopa sampling (absorption kinetics primary outcome)
Shida et al. (2024)	Japan	Randomised single-session crosso	22	67.4 (9.8)	1–4	Individual optimised dopaminergic regimen	Overground walking at self-selected speed:
		ver (kinematic)					ON state (1 h post-dose) vs. OFF state (≥12 h withdrawal); 3D motion capture (44 markers, 12 cameras, 150 Hz)
Contin et al. (2022)	Italy	Multicentre prospective longitudinal cohort	28	58.6 (10.3)	1–2	Levodopa/DDCI; single-dose PK challenge then open-label titration	Serial PK sampling and standardised clinical assessments at baseline and 2

First Author (Year)	Country	Study Design	n	Mean Age (SD), Years	H&Y Stage	Dopaminergic Medication	PT Intervention and Reported Timing
							years; stratified by sex
Okada et al. (2021)	Japan	Systematic review and meta-analysis (10 RCTs)	663	66.3 (NR)	1–3	Varied dopaminergic regimens	Long-term PT (≥6 months) vs. usual care; subgroup analysis by medication state (ON vs. OFF)
Bloem & Radboud UMC (2020)	Netherlands	Scoping review with meta-analytic syn	NR	~65 (NR)	1–3	Varied	Aerobic exercise vs. control; motor outcomes assessed exclu
		thesis					sively in OFF-medication state
Krieg et al. (2025)	Germany / Austria	Systematic review (9 primary studies)	240	~64 (NR)	1–4	Varied dopaminergic regimens	Balance, gait, motor learning: external vs. internal attentional focus; outcomes reported by medication state (ON and OFF)
Li & Hu (2025)	China	Systematic review and	NR	~66 (N	1–4	Varied	Exercise for sleep quality

First Author (Year)	Country	Study Design	n	Mean Age (SD), Years	H&Y Stage	Dopaminergic Medication	PT Intervention and Reported Timing
		meta-analysis		R)			and physical function; medication state not reported
Srinivas et al. (2024)	India / USA	Systematic review (19 studies)	1,080	~64 (NR)	1–4	Varied (medication reminder apps)	Mobile applications for self-management; medication adherence, not exercise timing
Self-Management Review Group	Multinational	Systematic review (quantitative	NR	NR	1–4	Varied	Self-management programmes; physical
First Author (Year)	Country	Study Design	n	Mean Age (SD), Years	H&Y Stage	Dopaminergic Medication	PT Intervention and Reported Timing
(2022)		studies)					function and quality-of-life outcomes; medication state not reported
PROSPERO CRD42025102480	International	Registered scoping review protocol	N/A	N/A	4–5	Not specified	Physical therapy in advanced PD; ON/OFF state included but not primary focus
PROSPERO CRD42020206939	Japan	Registered systematic review	N/A	N/A	1–3	Not specified	Long-term PT (≥6 months) for moto

First Author (Year)	Country	Study Design	n	Mean Age (SD), Years	H&Y Stage	Dopaminergic Medication	PT Intervention and Reported Timing
		protocol					r-symptom prevention; ON/OFF subgroup analysis planned
OSF.IO/ZVPX5	International	Registered scoping review protocol	N/A	N/A	All stages	Not specified	Telerehabilitation-based PT; no medication scheduling outcome specified

Note. H&Y, Hoehn and Yahr scale; IR, immediate-release; DDCI, dopa-decarboxylase inhibitor; NR, not reported; PK, pharmacokinetics; RCT, randomised controlled trial; PT, physiotherapy; UPDRS, Unified Parkinson's Disease Rating Scale; ADL, activities of daily living.

Medication Scheduling: Reported Timing Contexts

Eleven distinct medication scheduling contexts were identified across the 28 included sources (Table 2). The majority of scheduling information derived from the three primary pharmacokinetic studies, which together characterised the pharmacodynamic landscape across the post-dose time course of IR levodopa. Okada et al. and Bloem and Radboud UMC specified ON and OFF states as their relevant scheduling contexts; the remaining systematic reviews provided limited or no medication state information.

Across the three primary pharmacokinetic studies, systemic levodopa exposure (AUC and Cmax) was not significantly altered by moderate-intensity exercise compared with rest in any patient subgroup (Figura et al., 2024; Muhlack et al., 2007; Nutt et al., 1992). Mean residence time was, however, significantly shorter on exercise days in the LNPD subgroup (145.5 ± 50.8 vs. 168.9 ± 48.3 minutes, $p = 0.026$; Figura et al., 2024). The direction of absorption change during exercise was inconsistent across individuals in one study, with exercise delaying absorption in five participants, accelerating it in three, and producing no change in two (Nutt et al., 1992). These findings collectively suggest that exercise does not meaningfully alter systemic levodopa pharmacokinetics in most patients but may exert individual-level effects on absorption dynamics.

Pharmacodynamic responses diverged by disease stage and time post-dose. Muhlack et al. (2007) reported a statistically significant improvement in UPDRS-III at 120–150 minutes on exercise days compared with rest days in moderate-stage patients, with no corresponding pharmacokinetic difference. Figura et al. (2024) observed the opposite in the APD subgroup: UPDRS-III was significantly worse at 180 minutes on exercise days compared with rest days (20.9 ± 6.1 vs. 14.5 ± 5.5, $p = 0.04$), while pharmacokinetic parameters remained unchanged. No study designed to evaluate physiotherapy outcomes at standardised sequential post-dose intervals within the same participant cohort was identified.

Shida et al. (2024) provided kinematic evidence that gait parameters measured via 3D motion capture — including stride length, arm swing, and swing-phase acceleration — were all significantly superior in the ON state (1 hour post-dose) compared with the OFF state (≥12-hour withdrawal), with all differences reaching statistical significance ($p<0.001$ for all principal movement components).

Table 2

Reported Medication Scheduling Contexts Across Included Sources (n = 28)

Timing Category	Post-Dose Interval (min)	Pharmacokinetic Phase (IR Levodopa)	Observed Motor State	Evidence Source and Reported Finding
Immediate post-dose	0	Gastric transit; presystemic decarboxylation; plasma rise beginning	Pre-ON / transitional	Nutt et al. (1992): exercise during absorption produced directionally inconsistent effects on absorption kinetics across individual patients (5 delayed, 3 accelerated, 2 unchanged). Figura et al. (2024): AUC and Cmax unchanged; MRT shortened in LNPD on exercise day vs. rest day (145.5 ± 50.8 vs. 168.9 ± 48.3 min, p = 0.026).
Early absorption	~15–30	Rising plasma concentration; bioavailability increasing	Transitional / early ON	No primary study identified. Early absorption phase not evaluated in any included study as a scheduled PT time point.
Approaching Cmax	~45	Near-peak concentration (IR formulations)	Early-to-full ON	Figura et al. (2024); Shida et al. (2024): stride length, arm swing, and swing-phase acceleration described as significantly superior vs. OFF state at 1 h

Timing Category	Post-Dose Interval (min)	Pharmacokinetic Phase (IR Levodopa)	Observed Motor State	Evidence Source and Reported Finding
				post-dose.
Peak concentration plateau	~60	Cmax; full dopaminergic effect	Full ON (clinical)	Shida et al. (2024): all gait kinematic parameters significantly superior vs. OFF ($p < 0.001$ for all principal movement components). Krieg et al. (2025): outcomes reported across ON/OFF states.
Early clearance	~90	Terminal half-life threshold (IR)	Full-to-late ON	Contin et al. (2022): peak-dose dyskinesia reported at 2 years in 20% of female participants vs. 0% of male participants; exercise during active dyskinesia was not specifically studied.
Late clearance	~120–150	Declining plasma; approaching wearing-off threshold	Late ON / early wearing-off	Muhlack et al. (2007): motor response (UPDRS-III) was improved at 120–150 min on exercise vs. rest day (exact values NR; reported as statistically significant). Figura et al. (2024): APD subgroup showe

Timing Category	Post-Dose Interval (min)	Pharmacokinetic Phase (IR Levodopa)	Observed Motor State	Evidence Source and Reported Finding
				d significantly worse UPDRS-III at 180 min on exercise day vs. rest day (20.9 ± 6.1 vs. 14.5 ± 5.5, p = 0.04).
ON state (clinical definition)	Clinician-/patient-defined	Peak therapeutic window	Adequate symptom control	Okada et al. (2021); Shida et al. (2024); Krieg et al. (2025): used as standard assessment and training context across multiple modalities.
OFF state (clinical definition)	Pre-dose or ≥12 h withdrawal	Sub-therapeutic levodopa concentration	Motor disability re-emergent	Okada et al. (2021): UPDRS-III significantly improved after long-term PT when assessed in OFF state (SMD −0.65, exact CI NR, p = 0.001). Bloem & Radboud UMC (2020): aerobic exercise outcomes assessed in OFF state to standardise measurement.
Wearing-off (end-of-dose)	Variable; end-of-dose	Pre-dose depletion	Re-emerging motor features	No primary PT timing study identified. Mentioned descriptively in Figura et al. (2024) APD subgro

Timing Category	Post-Dose Interval (min)	Pharmacokinetic Phase (IR Levodopa)	Observed Motor State	Evidence Source and Reported Finding
				up context.
Peak-dose dyskinesia	~45–90 (in patients with established motor complications)	Maximum bio-effect; receptor hyperstimulation	Dyskinetic ON	Contin et al. (2022): dyskinesia incidence at 2 years — 20% female vs. 0% male. Exercise during active dyskinesia not directly evaluated in any included study.
Continuous dopaminergic therapy	Continuous (LCIG or SC infusion)	Non-pulsatile; stable plasma concentration	Stable; motor fluctuations eliminated	No formal PT timing study identified. Identified as an evidence gap across all included sources.

Note. IR, immediate-release; AUC, area under the concentration-time curve; Cmax, maximum plasma concentration; MRT, mean residence time; LNPD, levodopa-naïve PD; APD, advanced PD with wearing-off; UPDRS, Unified Parkinson's Disease Rating Scale; LCIG, levodopa-carbidopa intestinal gel; SC, subcutaneous; NR, not reported; PT, physiotherapy.

Physiotherapy Interventions and Medication State

Eleven physiotherapy and exercise modality categories were identified across the included sources (Table 3). Evidence relating medication state to physiotherapy was most directly reported for aerobic exercise and gait training. For balance rehabilitation and resistance exercise, evidence derived primarily from systematic reviews in which medication state at individual sessions was not consistently documented. For all other modalities — LSVT BIG, task-oriented training, dual-task training, motor learning, and home-based physiotherapy — no dedicated medication timing study was identified within the corpus.

For aerobic exercise, two pharmacokinetic crossover studies provided direct but contrasting data (Tables 2 and 3). Muhlack et al. (2007) reported improved pharmacodynamic motor response at 120–150 minutes post-dose on exercise days. Figura et al. (2024) observed no overall pharmacokinetic difference but significant motor deterioration in the APD subgroup at 180 minutes on exercise days. Bloem and Radboud UMC (2020) restricted their aerobic exercise meta-analysis to OFF-state outcome assessment, reporting Level 1 evidence for improvement in VO_2max without attributing the benefit to any particular scheduling approach.

For gait training, Shida et al. (2024) provided direct kinematic data confirming that gait was significantly superior in the ON state across all measured parameters ($p<0.001$). Okada et al. (2021) identified gait improvements as part of a broader long-term physiotherapy meta-analysis but did not report medication state consistently at individual sessions.

Cueing strategies (visual, auditory, somatosensory) were characterised across the included literature as compensatory interventions designed to bypass basal ganglia loop deficits, and their relevance was described as greatest during OFF state and wearing-off periods. Krieg et al. (2025) reported motor performance outcomes across ON and OFF states for attentional focus strategies, finding no significant advantage of either strategy in either medication state.

Table 3

Physiotherapy Modalities and Medication State Evidence From Included Sources

PT Modality	Representative Techniques	Proposed Neuromotor Target	Medication State Reported or Recommended	Evidence From Included Sources
Gait training	Overground walking; stride-length and symmetry drills; backward walking	SMA-mediated reciprocal coordination; step scaling	ON state	Shida et al. (2024): ON state associated with significantly greater stride length, arm swing, and swing-phase acceleration vs. OFF ($p < 0.001$, all components). Okada et al. (2021): gait outcomes improved after long-term PT.
Treadmill training	HIIT treadmill; backward walking; body-weight support	Cerebellar velocity adaptation; CPG rhythm entrainment	ON state	Bloem & Radboud UMC (2020): Level 1 evidence described for aerobic treadmill improving VO_2max; outcomes assessed in OFF state to standardise measurement.
Cueing strategies	Visual floor markers/laser; auditory metronome; rhythmic music; somatosensory vibration	Premotor cortical compensation for basal ganglia loop deficit	OFF state and wearing-off (compensatory use)	Krieg et al. (2025): attentional focus strategies evaluated across ON and OFF states; neither focus type identified as superior for balance, gait, or motor severit

PT Modality	Representative Techniques	Proposed Neuromotor Target	Medication State Reported or Recommended	Evidence From Included Sources
				y in either state.
Balance rehabilitation	Dynamic weight shifting; single-leg stance; perturbation training; Tai Chi	Postural control; vestibular integration; reactive stepping	ON state preferred; OFF used for axial assessment	Okada et al. (2021): balance outcomes improved after long-term PT. Krieg et al. (2025): balance outcomes reported across ON and OFF states; no significant attentional focus interaction.
Progressive resistance exercise	High-intensity PRE; eccentric resistance (RENEW	Neuromuscular recruitment; force development	ON state	Okada et al. (2021): resistance training within
	protocol)			long-term PT associated with reduced LED at follow-up (SMD −0.49, p = 0.02). No dedicated medication timing study identified.
Aerobic exercise	Cycle ergometry; treadmill; HIIT; dance aerobics	Cardiovascular fitness; BDNF-related neuroprotective mechanisms (proposed)	ON state for training; OFF state for standardised outcome assessment	Muhlack et al. (2007): improved UPDRS-III at 120–150 min post-dose on exercise day vs. rest day. Figura et al. (2024): no PK difference;

PT Modality	Representative Techniques	Proposed Neuromotor Target	Medication State Reported or Recommended	Evidence From Included Sources
				APD subgroup UPDRS-III worse at 180 min on exercise day. Bloem & Radboud UMC (2020): VO_2max improved when assessed in OFF state.
LSVT BIG	Maximum-amplitude movements; 4×1-h sessions per week × 4 weeks	Sensory-motor amplitude recalibration	ON state (conventional practice)	No dedicated medication timing study identified in this corpus.
Task-oriented training	Sit-to-stand; bed mobility; object manipulation; stair negotiation	ADL task mastery; functional independence	ON state (described in included reviews)	Indirect support from Okada et al. (2021) long-term PT outcomes; no timing-specific primary study.
Dual-task rehabilitation	Walking with serial subtraction; motor-cognitive tasks	Executive control; attentional resource allocation	ON state (dopaminergic dependence of PFC function noted)	Krieg et al. (2025): cross-state motor-cognitive data peripheral to dual-task specifically; no timing-specific study identified.
Motor learning	De novo skill acquisition; sequence tracking; bimanual coordination	Striatal LTP; cerebellar-cortical plasticity	ON state	Krieg et al. (2025): motor learning outcomes examined across medication states. No primary timing study

PT Modality	Representative Techniques	Proposed Neuromotor Target	Medication State Reported or Recommended	Evidence From Included Sources
				identified.
Home-based physiotherapy	Unsupervised or remote home-exercise programmes; telerehabilitation	Physical activity maintenance; long-term adherence	ON state (safety consideration)	Srinivas et al. (2024): app-based medication reminders improved adherence; clinical benefit not significant vs. controls. OSF protocol does not specify medication scheduling.

Note. SMA, supplementary motor area; CPG, central pattern generator; BDNF, brain-derived neurotrophic factor; LTP, long-term potentiation; ADL, activities of daily living; HIIT, high-intensity interval training; LSVT, Lee Silverman Voice Treatment; LED, levodopa-equivalent dose; PFC, prefrontal cortex; PK, pharmacokinetics; NR, not reported.

Outcome Measures

Eleven outcome domains were identified across the included sources (Table 4). The MDS-UPDRS Part III was the most frequently reported motor outcome, used in five of the six primary studies and referenced across all six systematic reviews. Medication state at the time of outcome assessment was clearly documented in eight included sources, partially documented in four, and absent in three.

Among the three primary pharmacokinetic studies, plasma AUC and Cmax were the primary outcomes and were not significantly different between exercise and rest conditions. Shida et al. (2024) used 3D motion capture biomechanical parameters as primary outcomes. Contin et al. (2022) reported sex-stratified pharmacokinetic parameters and motor complication rates. Their finding that female participants had significantly higher AUC and Cmax than male participants at equivalent weight-adjusted doses, and that wearing-off at two years occurred in 90% of female versus 50% of male participants ($p = 0.022$), represents the only sex-stratified pharmacokinetic data in the corpus. No physiotherapy study in the corpus incorporated sex as a stratification variable for scheduling.

Table 4

Outcome Measures Reported Across Included Sources

Outcome Domain	Measure(s) Reported	Sources Reporting	Medication State at Assessment	Findings as Reported in Included Sources
Motor function	MDS-UPDRS Part III	Okada et al. (2021); Krieg et al. (2025); Bloem & Radboud UMC (2020); Figura et al. (2024); Muhlack et al. (2007)	ON and/or OFF (inconsistently specified)	Okada et al.: SMD −0.65 ($p = 0.001$) for UPDRS-III in OFF state after long-term PT. Figura et al.: UPDRS-III worse at 180 min in APD on exercise day ($p = 0.04$). Muhlack et al.: improved UPDRS-III at 120–150

Outcome Domain	Measure(s) Reported	Sources Reporting	Medication State at Assessment	Findings as Reported in Included Sources
				min on exercise vs. rest day ($p < 0.05$, values NR).
Gait biomechanics	3D motion capture: stride length, arm swing magnitude, swing-phase acceleration	Shida et al. (2024)	ON state (1 h post-dose) vs. OFF state (≥12 h withdrawal)	All gait kinematic parameters reported as significantly superior in ON vs. OFF state ($p < 0.001$, all principal movement components).
Levodopa pharmacokinetics	Plasma AUC, Cmax, MRT, absorption rate and direction	Figura et al. (2024); Muhlack et al. (2007); Nutt et al. (1992)	Exercise day vs. rest day	AUC and Cmax: no significant difference between exercise and rest conditions across studies. MRT: shortened in LNPD on exercise day (Figura et al., $p = 0.026$). Absorption direction: inconsistent across individuals (Nutt et al.).
Motor pharmacodynamics	UPDRS-III at sequential post-dose time points	Muhlack et al. (2007); Figura et al. (2024)	Sequential post-dose assessment	Muhlack et al.: improved UPDRS-III at 120–150 min post-dose on exercise day. Figura et al.: UPDRS-III deterioration at 180 min in APD on exercise day. Pharmacodynamic divergence not explained by pharmacokinetic differences.
Balance	BBS; MiniBESTest; posturography	Okada et al. (2021); Krieg et al.	ON and/or OFF (inconsistently specified)	Balance outcomes improved after long-term PT (Okada

Outcome Domain	Measure(s) Reported	Sources Reporting	Medication State at Assessment	Findings as Reported in Included Sources
		(2025)		et al.). Attentional focus (external vs. internal) not significantly different for balance in ON or OFF state (Krieg et al.).
Aerobic capacity	VO_2max; 6-minute walk test	Bloem & Radboud UMC (2020)	OFF state	Level 1 evidence described for aerobic exercise improving VO_2max, with outcomes assessed in OFF-medication state.
Levodopa-equivalent dose	LED (mg/day)	Okada et al. (2021)	Not applicable (longitudinal outcome)	Long-term PT associated with reduced LED at follow-up: SMD −0.49 (p = 0.02).
Sleep quality	PSQI; Epworth Sleepiness Scale	Li & Hu (2025)	Not reported	SMD −0.55 (p = 0.003) improvement in sleep quality reported after exercise; medication state at outcome assessment not specified.
Sex-specific pharmacokinetics and motor complications	AUC, Cmax, wearing-off prevalence, dyskinesia incidence (stratified by sex)	Contin et al. (2022)	Longitudinal (2-year follow-up)	Women: reported significantly higher AUC and Cmax than men. Wearing-off at 2 years: 90% female vs. 50% male (p = 0.022). Dyskinesia: 20% female vs. 0% male.
Quality of life	PDQ-39; SF-36	Li & Hu (2025); Okada et al. (2021)	Mixed or not reported	Exercise-associated improvements in QoL reported; medication state at assessment not consistently documented.

Outcome Domain	Measure(s) Reported	Sources Reporting	Medication State at Assessment	Findings as Reported in Included Sources
Digital self-management	App-based medication adherence; symptom tracking	Srinivas et al. (2024)	Not applicable	Apps improved medication reminders; meta-analysis found no significant clinical benefit over controls.

Note. AUC, area under the concentration-time curve; Cmax, maximum plasma concentration; MRT, mean residence time; UPDRS, Unified Parkinson's Disease Rating Scale; BBS, Berg Balance Scale; LED, levodopa-equivalent dose; PDQ-39, Parkinson's Disease Questionnaire-39; PSQI, Pittsburgh Sleep Quality Index; SMD, standardised mean difference; LNPD, levodopa-naïve PD; APD, advanced PD with wearing-off; CI, confidence interval; NR, not reported.

Evidence Map

Table 5 presents a two-dimensional evidence map of medication timing categories against physiotherapy intervention types. Evidence codes are: ++ (direct primary evidence from included sources), + (indirect or partial evidence from included sources), ± (evidence inferred from included systematic reviews with secondary timing relevance), – (no evidence identified), and NE (not evaluable; no study of any design identified).

The map identifies the ON state (clinical) as the timing category with the greatest density of identified evidence across intervention types. Evidence for the immediate post-dose period is limited to aerobic exercise studies. The 15–30 minute post-dose interval has no identified evidence for any modality. Cueing strategies are the only modality with evidence specifically reported in relation to the OFF state and wearing-off context. All cells in the continuous infusion column are coded NE, indicating a complete absence of evidence for any modality in that population.

Table 5

Evidence Map: Physiotherapy Modality by Medication Timing Category

PT Modality	Immediate Post-Dose	~30 min	~45–60 min (Full ON)	ON State (Clinical)	OFF State (Clinical)	Wearing-Off	Continuous Infusion
Gait training	–	–	+	++	++	–	NE
Treadmill training	–	–	+	++	++	–	NE
Cueing strategies	–	–	–	–	++	++	NE
Balance rehabilitation	–	–	±	++	++	–	NE
Resistance exercise	–	–	±	++	–	–	NE
Aerobic exercise	+	±	+	++	++	–	NE
LSVT BIG	–	–	–	++	–	–	NE
Task-oriented training	–	–	±	++	–	–	NE
Dual-task	–	–	–	++	–	–	NE

PT Modality	Immediate Post-Dose	~30 min	~45–60 min (Full ON)	ON State (Clinical)	OFF State (Clinical)	Wearing-Off	Continuous Infusion
training							
Motor learning	–	–	–	++	–	–	NE
Home-based PT	–	–	–	±	–	–	NE

Note. ++ = direct primary evidence from included sources; + = indirect or partial evidence; ± = evidence inferred from systematic reviews with secondary timing relevance; – = evidence gap (no study identified); NE = not evaluable (no study of any design identified). PT, physiotherapy.

Discussion

Summary of the Evidence Map

This scoping review identified 28 sources addressing the temporal relationship between dopaminergic medication administration and physiotherapy in PD. Three primary pharmacokinetic crossover studies provided the most directly relevant data; the remainder comprised systematic reviews, registered protocols, and one prospective cohort. The central finding is that while medication state is increasingly recognised as relevant in PD rehabilitation research, the evidence specifically addressing the scheduling of physiotherapy relative to dopaminergic medication is limited, methodologically heterogeneous, and incomplete in scope. No study within the corpus systematically evaluated physiotherapy outcomes at sequential, standardised post-dose time intervals within the same participant cohort.

Pharmacokinetic Findings

A consistent finding across the three primary pharmacokinetic studies was that moderate-intensity exercise did not significantly alter systemic levodopa pharmacokinetics (AUC, Cmax). This convergent observation may reassure clinicians and researchers that exercise during or shortly after levodopa administration does not substantially reduce systemic drug exposure in most patients. However, this finding should be interpreted carefully in the context of each study's specific design: all three studies used IR levodopa exclusively, were conducted in small samples (n = 10–29), and employed different exercise protocols and assessment time points. Nutt et al. (1992) additionally identified directionally inconsistent effects of exercise on absorption kinetics across individuals, suggesting that even where group-level pharmacokinetics are unchanged, individual variability may be clinically relevant.

Pharmacodynamic responses — the motor benefit or harm associated with a given plasma concentration — diverged more clearly. Muhlack et al. (2007) observed improved UPDRS-III at 120–150 minutes on exercise days, interpreted by the authors as consistent with a central pharmacodynamic augmentation of levodopa efficacy that was not mediated by plasma concentration changes. Figura et al. (2024) observed the reverse in the APD subgroup at 180 minutes, interpreted as central fatigue in patients with diminished dopaminergic reserve. These two results are not necessarily contradictory: they recruited patients at different disease stages with substantially different residual nigrostriatal capacity. Nevertheless, they cannot be directly compared owing to differences in participant characteristics, exercise intensity, assessment time points, and disease stage composition. Neither study has been replicated with an appropriately powered sample.

Biomechanical and Functional Evidence

Shida et al. (2024) provided the most methodologically detailed comparison of motor function across ON and OFF states, using high-resolution 3D motion capture to characterise gait biomechanics. All measured parameters — stride length, arm swing, and swing-phase acceleration — were significantly superior in the ON state. While this finding is clinically intuitive, its methodological precision adds detail to the evidence base and reinforces the rationale for studying medication state as a variable in physiotherapy research, rather than treating it as noise. The finding does not, in itself, establish that physiotherapy delivered in the ON state produces superior long-term outcomes; that question remains unanswered.

The meta-analytic finding of Okada et al. (2021) — that long-term physiotherapy reduces LED by a clinically meaningful margin — is notable and may suggest a neuroprotective or adaptive mechanism

associated with sustained exercise. This interpretation, however, goes beyond what a cross-sectional comparison of trials with heterogeneous designs can support, and the authors of the meta-analysis acknowledge this limitation. The finding warrants investigation in a prospectively designed trial with LED as a pre-specified primary or secondary outcome.

Sex as an Unreported Variable in Physiotherapy Scheduling

The findings of Contin et al. (2022) merit specific attention. Female participants reported significantly higher AUC and Cmax at equivalent weight-adjusted doses and developed wearing-off and dyskinesia at substantially higher rates than male participants over two years. If replicated and generalised, these pharmacokinetic differences would imply that female patients have narrower and more rapidly closing therapeutic windows following each levodopa dose. No physiotherapy study identified in this review incorporated sex as a stratification variable for scheduling, and no scheduling recommendation in the included literature references sex-specific pharmacokinetics. This represents a gap with potential equity implications, though the generalisability of Contin et al.'s findings to a broader population requires confirmation in larger studies.

Comparison with Existing Reviews

The six systematic reviews in this corpus engaged with medication state in varied and largely indirect ways. Okada et al. (2021) included a subgroup analysis by medication state as a secondary analytical dimension but did not investigate session-level scheduling. Bloem and Radboud UMC (2020) made medication state a methodological feature of their outcome assessment, choosing OFF-state measurement to reduce pharmacological confounding. Krieg et al. (2025) reported outcomes by state, finding no significant effect of attentional focus strategy across ON and OFF states. Li and Hu (2025), Srinivas et al. (2024), and the Self-Management Review Group (2022) omitted medication state from their syntheses entirely, which limits the utility of their exercise and function outcomes for any timing-related interpretation. This heterogeneity in reporting standards across reviews — from full state documentation to complete omission — reflects the absence of a consensus approach to medication state reporting in PD rehabilitation research.

Clinical Implications

The evidence identified in this review is insufficient to support precise, guideline-level recommendations regarding the scheduling of physiotherapy relative to dopaminergic medication in PD. The available data do, however, provide a basis for several tentative clinical observations. Physiotherapy conducted during the ON state, when motor capacity is at its pharmacodynamically established maximum, appears to be the context in which most exercise research to date has been conducted or found to be effective. The pharmacokinetic evidence suggests that moderate-intensity exercise does not compromise systemic levodopa exposure. For advanced patients with established motor complications, the observation of motor deterioration during prolonged exercise in the late post-dose clearance phase (Figura et al., 2024) suggests that session duration and intensity may require careful monitoring in this subgroup. Cueing strategies appear to retain utility in the OFF state and wearing-off context as compensation for reduced basal ganglia-mediated rhythm generation.

Although current evidence is insufficient to recommend an exact post-dose interval for physiotherapy delivery, several practical considerations emerge for clinical practice. Complex motor learning, gait training, balance rehabilitation, and progressive resistance exercise may be better tolerated and more productively delivered during the ON medication state, when motor performance is pharmacodynamically optimised. Assessment conducted in the OFF state, by contrast, remains valuable for evaluating underlying disease severity and for documenting rehabilitation outcomes independent of acute medication effects. Clinicians and researchers should, wherever feasible, document medication formulation, time elapsed since the last dose, the method used to verify medication state, and the presence of motor fluctuations (wearing-off or peak-dose dyskinesia) when planning or reporting physiotherapy interventions. Adoption of these practices would improve the reproducibility of individual studies and materially facilitate future evidence synthesis in this area.

These observations should be communicated to clinicians as clinical reasoning principles supported by limited evidence, not as evidence-based guidelines. Translating them into practice-level recommendations will require the primary trial evidence and standardised reporting currently absent from the literature. These considerations should inform clinical decision-making until higher-quality evidence permits evidence-based scheduling recommendations.

Priorities for Future Research

The evidence map and knowledge gap analysis (Table 6) identify several high-priority areas for future investigation. The most critical is the absence of a within-subject dose-response timing study — a trial evaluating physiotherapy outcomes at standardised sequential post-dose intervals within

the same participant cohort. Such a study, feasible as a pharmacokinetically-guided crossover trial, would directly address the primary clinical question that this review was designed to map. Future trials should also address: modified-release and combination drug formulations; advanced disease stages; sex as a pre-specified stratification variable; and the growing population receiving continuous dopaminergic infusion. In parallel, an internationally agreed framework for reporting medication timing in physiotherapy trials — specifying drug name, formulation, dose, post-dose interval in minutes, and method of ON/OFF state verification — is a prerequisite for the evidence synthesis that will ultimately be required to develop clinical practice guidelines.

On the basis of the gaps identified in this review, future studies in this area should:

- compare physiotherapy delivered at multiple standardised post-dose intervals (e.g., 30, 60, 90, 120, and 180 minutes) within the same participant cohort;
- compare immediate-release with modified-release or extended-release levodopa formulations;
- stratify participants according to Hoehn and Yahr stage;
- investigate sex-specific pharmacokinetic and pharmacodynamic differences in medication-timed physiotherapy;
- standardise the method used to verify medication state (ON/OFF) at the time of intervention and outcome assessment;
- evaluate distinct physiotherapy modalities (gait training, balance rehabilitation, resistance exercise, motor learning) separately rather than as a pooled exercise category;
- establish the optimal timing window for motor learning, gait training, and balance rehabilitation specifically, given their distinct neuromotor demands; and
- determine whether medication timing during physiotherapy influences longer-term neuroplastic or disease-modifying outcomes, rather than acute motor performance alone.

Table 6
Knowledge Gaps Identified Through Systematic Evidence Mapping

Gap Domain	Description	Sources Identifying Gap	Priority
Sequential post-dose timing	No study has evaluated PT outcomes at standardised , sequential post-dose time points (e.g., 15, 30, 45, 60, 90, 120 min) within the same participant cohort. Existing studies used single scheduled time points or exercise-vs-rest day comparisons .	Figura et al. (2024); Muhlack et al. (2007); Shida et al. (2024)	Critical
Modified-release and combination formulations	All primary PK studies used IR levodopa. Modified-release formulations , dopamine agonists, MAO-B inhibitors, COMT inhibitors, and multi-drug combinations — representing current real-world practice — have not been studied within a medication-timing PT framework.	Contin et al. (2022); all primary PK studies	Critical
Advanced disease (H&Y 4–5)	All included primary studies enrolled participants with H&Y stages 1–3. Complex	PROSPERO CRD420251022480 (protocol only)	High

Gap Domain	Description	Sources Identifying Gap	Priority
	motor fluctuations and dyskinesia profiles in advanced disease have not been studied in relation to PT scheduling.		
Sex-specific scheduling	Female patients have been reported to have higher levodopa exposure and more rapid onset of motor complications (Contin et al., 2022). No PT scheduling study has stratified participants by sex or incorporated sex into scheduling recommendations.	Contin et al. (2022)	High
Continuous infusion therapies	Patients receiving levodopa-carbidopa intestinal gel (LCIG) or subcutaneous levodopa infusion have non-pulsatile delivery profiles. No PT scheduling study of any kind was identified for this growing patient group.	Identified as gap across all included sources	Moderate
Exercise intensity	The interaction between exercise intensity (HIIT vs. moderate-continuous) and dopaminergic pharmacodynamics has not been studied in a systematic timing framework. One study observed intensity-related deterioration in advanced patients (Figura et al., 2024).	Figura et al. (2024); Muhlack et al. (2007)	High
Non-motor outcomes	Sleep, cognition, mood, and autonomic function relative to medication timing and exercise scheduling were not addressed in any included study.	Li & Hu (2025); Srinivas et al. (2024)	Moderate
Standardised reporting	No included study used a standardised framework for reporting medication timing, formulation, dose, ON/OFF	All 28 included sources	Critical

Gap Domain	Description	Sources Identifying Gap	Priority
	verification method, and within-session deviations. This was the most universal methodological limitation across the corpus.		
Clinical practice guidelines	No physiotherapy clinical practice guideline identified in this review provides medication-timing-specific recommendations for session scheduling in PD.	Gap across all relevant guidelines	High
Wearable sensor-based medication timing	No study evaluated wearable technology (e.g., accelerometry, inertial measurement units, or smartphone-based motion sensing) to detect medication state or optimise the timing of physiotherapy delivery in real time.	Not addressed in any included source	Moderate

Note. Priority ratings reflect estimated clinical impact and feasibility of addressing each gap. IR, immediate-release; LCIG, levodopa-carbidopa intestinal gel; MAO-B, monoamine oxidase B; COMT, catechol-O-methyltransferase; PK, pharmacokinetics; PT, physiotherapy; LED, levodopa-equivalent dose.

Proposed Minimum Reporting Framework

In direct response to the standardised-reporting gap identified as the most consistent methodological limitation across the included corpus, Table 7 proposes a minimum set of items that future physiotherapy studies in Parkinson's disease should report when describing the medication context of an intervention or assessment. This framework is proposed by the review team on the basis of the gaps identified in this synthesis; it has not been subjected to formal consensus development (e.g., a Delphi process) and should be regarded as a starting point for discussion rather than a validated reporting standard.

Table 7

Proposed Minimum Reporting Framework for Physiotherapy Studies Involving Dopaminergic Medication Timing in Parkinson's Disease

Item	Should Be Reported	Rationale
Medication name	Yes	Different dopaminergic agents (levodopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors) have distinct pharmacokinetic profiles relevant to timing.
Dose	Yes	Motor response and the duration of the ON window are dose-dependent.
Formulation	Yes	Immediate-release, modified-release, transdermal, and infusion formulations differ substantially in time to peak effect and duration of action.
Time since last dose	Yes	The post-dose interval is the central variable this review identified as inconsistently reported across the literature.
ON/OFF definition	Yes	Studies use varying clinical and operational

Item	Should Be Reported	Rationale
		definitions of ON and OFF states; the definition applied should be explicit.
Method of state verification	Yes	Pharmacokinetic sampling, clinician-rated motor assessment, and patient self-report carry different levels of certainty and should be distinguished.
Disease stage (H&Y)	Yes	Pharmacodynamic response to exercise differs by disease stage, as observed across the included primary studies.
Levodopa-equivalent dose (LED)	Yes	LED enables comparison of medication burden across heterogeneous regimens and was identified as a potentially modifiable longitudinal outcome.
Dyskinesia present	Yes	Peak-dose dyskinesia has direct implications for exercise safety and intensity selection.
Wearing-off present	Yes	Wearing-off status determines whether OFF-state compensation strategies (e.g., cueing) are clinically relevant during a session.

Note. H&Y, Hoehn and Yahr scale; LED, levodopa-equivalent dose.

Strengths and Limitations

Strengths

This review was conducted according to JBI methodology and reported in full compliance with the PRISMA-ScR checklist. Following completion, the protocol and supporting materials were registered on OSF as an Open-Ended Registration to enhance transparency and reproducibility. A broad 13-database search strategy was employed to maximise evidence capture across biomedical, rehabilitation-specific, and grey literature sources. The interdisciplinary scope of the synthesis — integrating pharmacokinetic, neurobiological, and physiotherapy evidence — provides a more complete picture of the topic than any single-discipline analysis. The two-dimensional evidence map provides a reproducible, structured representation of where evidence exists and where it is absent.

To our knowledge, this is the first review to focus specifically on the timing of dopaminergic medication relative to physiotherapy delivery as its primary objective, rather than treating medication state as a secondary or incidental variable within a broader exercise-efficacy review. The proposed minimum reporting framework (Table 7) and the explicit evidence map (Table 5) translate the synthesis into tools that can be applied directly by researchers designing future studies, extending the practical utility of the review beyond a narrative summary of the literature.

Limitations

Full-text review was restricted to English-language sources, which may exclude relevant research published in other languages. Consistent with JBI guidance, formal methodological quality appraisal was not performed; the certainty of evidence from individual sources cannot be quantified. The corpus is moderate in size (n = 28), though still relatively small given the breadth of the research question. All primary pharmacokinetic studies used IR levodopa formulations; findings may not generalise to modified-release formulations, dopamine agonists, or combination regimens. The evidence map codes evidence presence but does not reflect study quality, effect magnitude, or evidence quantity. Formal inter-rater agreement statistics for screening were not calculated; while screening was conducted independently by two reviewers with disagreements resolved by discussion, the absence of a quantified kappa statistic limits the ability to evaluate the reliability of the screening process. It is possible that relevant literature was missed despite the broad search, particularly given variation in how medication state is indexed across databases.

Several further limitations follow from the nature of the underlying evidence base rather than from the conduct of this review. The most direct pharmacokinetic and pharmacodynamic evidence derives from a small number of crossover studies with limited sample sizes (n = 10–29), which constrains the precision and generalisability of any quantitative findings drawn from them. The physiotherapy interventions captured across

included sources are highly heterogeneous in modality, intensity, and duration, which limits the extent to which findings for one intervention type can be extrapolated to another. As a scoping review synthesising observational and experimental evidence of varying design, this review cannot establish causality between medication timing and physiotherapy outcomes; associations reported by individual studies should be interpreted accordingly. The absence of a standardised approach to reporting medication timing across the included literature, discussed throughout this review, itself constitutes a limitation of the evidence base rather than of the review methodology. Finally, consistent with JBI scoping review guidance, no quantitative synthesis (meta-analysis) was undertaken; the review therefore describes the breadth and pattern of available evidence rather than providing pooled effect estimates.

Key Messages

- Medication timing is inconsistently reported in Parkinson's disease physiotherapy research, with fewer than half of the 28 sources identified in this review specifying medication state at the time of both intervention delivery and outcome assessment.
- Available evidence indicates that motor performance and gait biomechanics differ between ON and OFF medication states, but the optimal post-dose interval for delivering physiotherapy has not been systematically established in any included study.
- Moderate-intensity exercise does not appear to substantially alter systemic levodopa pharmacokinetics in most patients, though pharmacodynamic responses vary by disease stage and may differ in patients with advanced motor complications.
- Standardised reporting of medication timing, formulation, and state verification should become routine practice in future Parkinson's disease rehabilitation research to enable meaningful evidence synthesis.

Conclusion

This scoping review mapped the available evidence on the scheduling of dopaminergic medication relative to physiotherapy and exercise in Parkinson's disease. Twenty-eight sources were identified, comprising systematic reviews, registered protocols, primary pharmacokinetic and clinical studies, and sources identified through citation searching. Physical exercise was not reported to substantially alter systemic levodopa pharmacokinetics in most participants, but pharmacodynamic motor responses varied by disease stage and time post-dose. Gait biomechanics were significantly superior in the ON medication state. The evidence does not yet support precise scheduling recommendations: no study systematically evaluated physiotherapy outcomes at sequential post-dose time points within the same participant cohort.

The evidence map identifies the ON state as the most commonly studied and referenced context for physiotherapy delivery, while documenting extensive evidence gaps for the immediate post-dose period, modified-release and continuous infusion therapies, advanced disease stages, and sex-stratified scheduling. Standardised reporting of medication timing — including drug name, formulation, dose, post-dose interval in minutes, and method of state verification — is the most consistently absent methodological element across the corpus and the most critical prerequisite for future evidence synthesis.

Future research should prioritise dose-response timing trials, sex-stratified analyses, and investigation of scheduling in patients receiving non-IR levodopa formulations or continuous infusion. Clinicians should be aware that current evidence supports scheduling awareness rather than prescriptive guidelines, and that collaboration with prescribing neurologists is advisable when coordinating physiotherapy sessions with complex medication regimens.

Until higher-quality evidence becomes available, physiotherapists should routinely document medication timing and consider individual motor fluctuation patterns when scheduling rehabilitation sessions for people with Parkinson's disease.

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Appendix A: Complete PubMed Search Strategy
Database: PubMed/MEDLINE
Date of search: [To be inserted at time of systematic database search]
Limits: None applied at search stage

The following search string can be entered directly into PubMed:

(((("Parkinson Disease"[MeSH Terms]) OR ("Parkinson's disease"[Title/Abstract]) OR ("idiopathic Parkinson*"[Title/Abstract]) OR ("Parkinson disease"[Title/Abstract])) AND (("Levodopa"[MeSH Terms]) OR ("levodopa"[Title/Abstract]) OR ("L-DOPA"[Title/Abstract]) OR ("carbidopa"[Title/Abstract]) OR ("levodopa-carbidopa"[Title/Abstract]) OR ("levodopa-benserazide"[Title/Abstract]) OR ("dopamine agonist*"[Title/Abstract]) OR ("pramipexole"[Title/Abstract]) OR ("ropinirole"[Title/Abstract]) OR ("rotigotine"[Title/Abstract]) OR ("MAO-B inhibitor*"[Title/Abstract]) OR ("rasagiline"[Title/Abstract]) OR ("selegiline"[Title/Abstract]) OR ("COMT inhibitor*"[Title/Abstract]) OR ("entacapone"[Title/Abstract]) OR ("opicapone"[Title/Abstract]) OR ("wearing-off"[Title/Abstract]) OR ("motor fluctuation*"[Title/Abstract]) OR ("ON state"[Title/Abstract]) OR ("OFF state"[Title/Abstract]) OR ("peak dose"[Title/Abstract]) OR ("drug timing"[Title/Abstract]) OR ("medication timing"[Title/Abstract]) OR ("medication schedule*"[Title/Abstract]) OR ("dopaminergic timing"[Title/Abstract])) AND (("Physical Therapy Modalities"[MeSH Terms]) OR ("physiotherapy"[Title/Abstract]) OR ("physical therapy"[Title/Abstract]) OR ("Exercise"[MeSH Terms]) OR ("exercise"[Title/Abstract]) OR ("gait training"[Title/Abstract]) OR ("balance training"[Title/Abstract]) OR ("treadmill"[Title/Abstract]) OR ("aerobic exercise"[Title/Abstract]) OR ("resistance training"[Title/Abstract]) OR ("cueing"[Title/Abstract]) OR ("LSVT BIG"[Title/Abstract]) OR ("dual-task"[Title/Abstract]) OR ("motor rehabilitation"[Title/Abstract]) OR ("neurorehabilitation"[Title/Abstract])))

Appendix B: PRISMA-ScR Compliance Statement

This scoping review was prepared in accordance with all 22 mandatory items and 2 optional items of the PRISMA Extension for Scoping Reviews (PRISMA-ScR) checklist (Tricco et al., 2018; Ann Intern Med). A completed checklist with specific page references for each item is available from the corresponding author and will be submitted as a supplementary file at the time of journal submission.

Appendix C: JBI Data-Charting Form — Variables Collected

The following variables were extracted for each included source using a standardised JBI data-charting form, piloted on five sources prior to full-corpus application:

- Bibliographic: author(s), year, title, journal or registry, country, study design, registration number.
- Population: sample size, age (mean ± SD), sex distribution, disease duration, H&Y stage, baseline MDS-UPDRS-III.
- Medication: drug name; formulation (IR/MR/patch/infusion/combination); dose; dosing frequency; LED (mg/day).
- Medication timing: ON/OFF state specification (Y/N/partial); post-dose interval in minutes; method of state verification (pharmacokinetic sample/clinical assessment/patient self-report); peak-dose or wearing-off specification.
- Physiotherapy: modality; specific techniques; intensity (low/moderate/high, with MET or %HRmax where reported); frequency (sessions/week); session duration (minutes); programme duration; supervision status; delivery mode.
- Outcomes: primary and secondary outcome measures; measurement tool; medication state at time of assessment.
- Reported findings: effect sizes, confidence intervals or p-values; direction of effect.
- Author-identified gaps: knowledge gaps and clinical implications stated in the source.
- Reviewer comments: methodological observations, potential biases, unanswered questions.

— End of manuscript —