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Therapeutic Spectrum of Intermittent Apomorphine in Parkinson's Disease: Neuropsychiatric, Behavioral, and Cognitive Analyses

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ABSTRACT

Introduction: Intermittent subcutaneous (SC) apomorphine is a fast-acting dopamine agonist used in the management of motor fluctuations in advanced Parkinson's disease (PD). While its motor benefits are well established the effects on non-motor domains and the modifying role of chronological age remain less certain. This prospective observational study aimed to evaluate the effectiveness of intermittent SC apomorphine on motor and non-motor outcomes in idiopathic PD patients with persistent motor fluctuations despite optimized oral therapy, and to examine whether age influenced therapeutic response.

Methods: Thirty-five idiopathic PD patients treated with intermittent SC apomorphine were followed for twelve weeks and assessed at baseline and week 12. Motor outcomes included Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III and diary-based daily "off" and "on" time without dyskinesia. Non-motor outcomes comprised the Montreal Cognitive Assessment (MoCA), Beck Depression Inventory (BDI), Parkinson's Disease Questionnaire (PDQ-8), and Parkinson's Disease Sleep Scale (PDSS). Subgroup analyses compared outcomes between patients aged <45 and ≥45 years and interaction effects were explored.

Results: MDS-UPDRS Part III scores improved from 45.71 (SD 11.93) to 29.86 (SD 12.24) (p <0.001). Mean daily "off" time decreased from 5.60 (1.65) to 2.26 (0.95) hours, while "on" time without dyskinesia raise from 10.34 (1.76) to 13.89 (0.93) hours (both p <0.001). Non-motor outcomes also improved: BDI declined from 23.03 (5.70) to 18.09 (4.87), MoCA increased from 15.74 (5.51) to 18.03 (6.05), and PDQ-8 from 22.80 (5.60) to 17.54 (5.84) (all p <0.001). Parkinson's disease sleep scale showed no significant change. No significant age-by-treatment interaction effects were detected.

Conclusion: Intermittent subcutaneous apomorphine was associated with significant improvements in multidimensional aspects, including motor and various non-motor domains, which are closely related to cognition, mood, and quality of life in PD. Benefits were consistent across age groups, indicating chronological age does not influence efficacy.

Keywords: age-stratified analysis, cognitive function, intermittent subcutaneous apomorphine injection, motor fluctuations, non-motor symptoms, Parkinson's disease

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INTRODUCTION

Parkinson's disease (PD) is a complex neurodegenerative process that is not limited to motor symptoms (1,2). In addition to motor complications, non-motor symptoms such as sleep disorders, depression, cognitive decline, and behavioural dysfunction are frequently observed (2–4). Furthermore, clinical experience and large cohort studies have shown that the burden of non-motor symptoms is the primary determinant of reduced quality of life in PD patients (4,5).

While levodopa and device-aided strategies, including intermittent apomorphine self-injection clearly ameliorate motor symptoms in many PD patients, the evidence is heterogeneous regarding their effects on specific non-motor domains, notably cognition and affect, thereby motivating targeted, hypothesis-driven investigations into non-motor outcomes (6,7). Standard dopaminergic treatments are effective in controlling motor symptoms, particularly in early disease stages,

Highlights

- **Intermittent SC apomorphine boosts motor and cognitive outcomes in PD.**
- **Efficacy of intermittent SC apomorphine is independent of age and disease onset.**
- **Intermittent SC apomorphine improves mood and executive function in PD reliably.**
- **Treatment reduces motor fluctuations and increases functional "on" time in PD.**
- **Findings support apomorphine as a personalized PD care strategy.**

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but they have significant limitations in the long term (8). For example, pulsatile oral treatment has been reported to cause progressive motor complications, and some levodopa and similar drugs have been reported to cause neuropsychiatric side effects such as cognitive impairment, sleep attacks, or impulse control disorders (9), and to improve some non-motor symptoms such as pain, fatigue, and anxiety, while causing undesirable effects such as significant orthostatic hypotension and somnolence (10). This situation has necessitated new approaches in PD management that go beyond motor gains.

Apomorphine, a non-ergoline dopamine agonist with high affinity for D_1–D_3 receptors, demonstrates a pharmacological profile that closely resembles that of levodopa. Due to its lipophilicity and rapid central uptake, clinical effects start within minutes after subcutaneous administration and typically persist for 1–2 hours (11). These kinetics make intermittent subcutaneous (SC) apomorphine especially suitable for the acute reversal of unpredictable "off" episodes, whether delivered by a patient autoinjector for rescue dosing or by a portable pump as a continuous SC apomorphine infusion (CSAI). Clinical series and trials document rapid, dose-dependent motor benefit and substantial reductions in daily off time, with infusion approaches showing efficacy comparable to other device-aided therapies for selected patients, while preclinical studies suggest additional modulatory effects on oxidative-stress pathways and ferroptosis-like mechanisms that remain hypothesis-generating rather than proven neuroprotection in humans (12,13).

Young-onset PD (YOPD), which begins before the age of 45, differ from late-onset patients in terms of clinical course and neurochemical dynamics (14,15). These findings support the classification of YOPD as a biologically distinct form of PD with differential treatment responsiveness. Age-related differences in therapeutic response in PD are attracting increasing attention, particularly in the context of young-onset cases. Studies on apomorphine treatment do not provide that clearly compare age-related clinical response differences in non-motor symptom domains.

The primary objective of this prospective observational cohort study was to quantify the clinical effects of a 12-week course of intermittent SC apomorphine administration on motor especially in patients with functionally significant motor fluctuations and non-motor functions. Our primary hypothesis was that treatment would produce a statistically and clinically meaningful increase in daily "on" time and "on" time without troublesome dyskinesia, decrease in "off" time, and an improvement in MDS-UPDRS Part III scores at 12 weeks compared with baseline. Secondary hypotheses specified measurable improvements in cognitive, mood, and health-related quality of life outcomes, as well as a reduction in levodopa equivalent daily dose (LEDD). Finally, an exploratory aim was to examine whether short-term response trajectories differ by age group, with a pre-specified comparison of age <45 years vs ≥45 years.

METHODS

Study Design and Participants

This 12-week prospective study enrolled 35 individuals with idiopathic PD, according to Queen Square Brain Bank criteria, staged by the Movement Disorder Society–Unified Parkinson's Disease Rating Scale III (MDS-UPDRS III) and the Modified Hoehn & Yahr (mH&Y) scale. Participants had advanced PD with motor fluctuations despite optimized oral therapy. Motor diaries were kept throughout follow-up to record consecutive 30-minute epochs during each waking day and were reviewed at predefined visits at baseline, 24 hours, week 1, week 4, and week 12 by two independent movement disorder clinicians (EDU and the external specialist). Discordant entries were reconciled by a structured telephone interview within 48 hours. Diary data underwent double data entry and were cross-checked. An experienced apomorphine nurse conducted injection training, adherence checks, and in-person follow-ups (Fig. 1). Blood pressure and 12-lead ECGs were obtained by the responsible clinician (EDU). Adverse events were recorded at each visit via patient diaries and spontaneous reports, and coded using a prespecified checklist by system-organ class; severity was graded as mild, moderate, or severe, and relationship to apomorphine was adjudicated by the treating clinician. Injection-site reactions (such as erythema, pain, and nodules) were specifically queried at each visit. Serious adverse events were defined according to the International Council for Harmonization (ICH) Good Clinical Practice (GCP) criteria. Written informed consent was obtained, and the protocol received local ethics approval (E-2023-71).

Inclusion criteria: Age 18–80 years; idiopathic PD ≥2 years; dominant diurnal motor fluctuations and "off" periods despite ≥4 daily levodopa

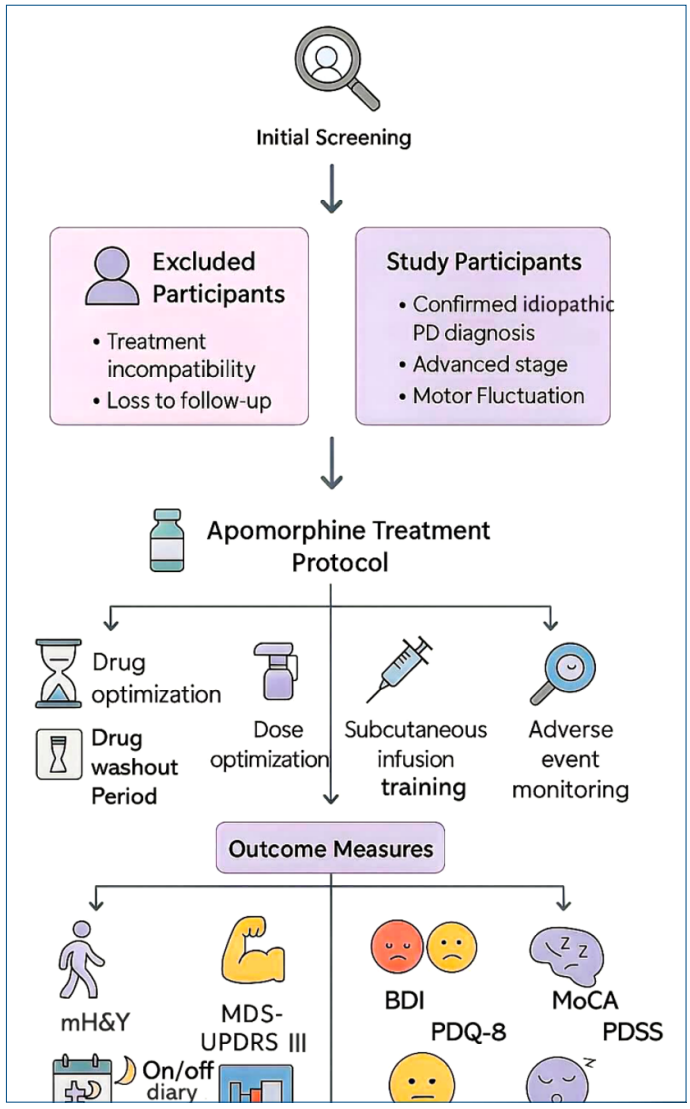

Figure 1. Study design flowchart of the apomorphine treatment protocol. Participants underwent initial screening, exclusion, and inclusion based on predefined criteria, followed by treatment phases and outcome assessments (PD: Parkinson's disease; MDS-UPDRS: movement disorder society – unified Parkinson's disease rating scale (parts III); MoCA: Montreal cognitive assessment; BDI: Beck depression inventory; PDQ-8: Parkinson's disease questionnaire-8; PDSS: Parkinson's disease sleep scale; mH&Y: modified Hoehn and Yahr).

doses; ≥4 h off + ≥2 h on-dyskinesia per day; mH&Y stage ≥2; ability to self-administer SC apomorphine for 12 weeks, accurately record motor and dyskinesia events.

Exclusion criteria: Included secondary or atypical parkinsonism, history of deep brain stimulation or intestinal levodopa-carbidopa gel use prior apomorphine therapy, significant psychiatric illness, cardiovascular abnormalities, or laboratory deviations. Patients with MRI or genetic findings suggestive of atypical parkinsonism or Parkinson-plus syndromes were excluded, in line with previously published protocols. The <45 years cut-point was prespecified to ensure adequate subgroup size and is consistent with prior age-stratified analyses. Sample size (n=35) was planned with G*Power 3.1.9.7 for the primary endpoints, based on an expected within-subject effect size dz=1.064 (two-tailed, α=0.05, power=0.956); the target effect size was informed by prior apomorphine response reports.

Medication and Titration Protocol

All procedures were supervised by a movement-disorder neurologist (EDU); trained nursing staff performed administration and patient/caregiver self-administration training. Baseline safety included complete blood count, biochemistry, thyroid panel, ECG and blood pressure. Per local practice, domperidone 20 mg was given 2 h before the first apomorphine exposure. Dopaminergic medications were withheld overnight (≥12 h) for initial response testing.

Apomorphine responsiveness test (bolus): SC apomorphine test injections were administered in 1.5 mg increments at 45-min intervals up to a maximum 9 mg, or until a full "on" response with tolerable adverse effects was observed (16).

SC apomorphine titration and maintenance protocol: Titration success was defined by motor response (MDS-UPDRS III, mH&Y) comparable to levodopa. Maintenance dose was evaluated at baseline, 24 h post-first dose, and at weeks 1, 4, and 12. Adjustments were allowed at week 1. A stepwise reduction of oral dopaminergic medications was implemented, prioritizing dopamine agonists and MAO-B inhibitors, followed by levodopa dosing and frequency. Following titration, an 8-week dose-stable maintenance period ensued; final assessments occurred at week 12.

Patients maintained a diary documenting 30-minute intervals of motor state (on/off/dyskinesia), sleep, and if possible blood pressure, and ECG readings. Adverse events were monitored at each visit, and dosing details, injection frequency (times/day), apomorphine dose (mg), and changes in levodopa and Levodopa equivalent daily dose (LEDD) were recorded (Fig. 2). Baseline LEDD values were calculated from the actual antiparkinsonian medication regimens documented at the time of apomorphine initiation by converting each agent to levodopa equivalents and summing these contributions; conversion factors were applied using the publicly available LEDD calculator on ParkinsonsMeasurement. org, which implements the standard Tomlinson et al. (17) conversion table. Prior to initiation of apomorphine, each participant underwent a focused specialist medication review by a movement-disorder neurologist (EDU): this review assessed adherence, timing, symptom-related dosing, and the potential for dose/timing adjustments or adjunctive therapies according to best clinical practice. For analysis, the LEDD corresponding to the regimen in place at the time of apomorphine initiation was used as the "baseline" LEDD.

Outcome Measures

All scales were primarily administered in randomized order by corresponding author (EDU), and re-administered by an external neuropsychologist (for non-motor assessments) and an external movement disorders specialist (for motor assessments) blinded to all data. Inter-rater reliability was ensured.

Motor assessments: Included MDS-UPDRS III and mH&Y during the 'on' state. Motor complications such as frequency, duration, severity of off periods and dyskinesia were measured via MDS-UPDRS IV and patient

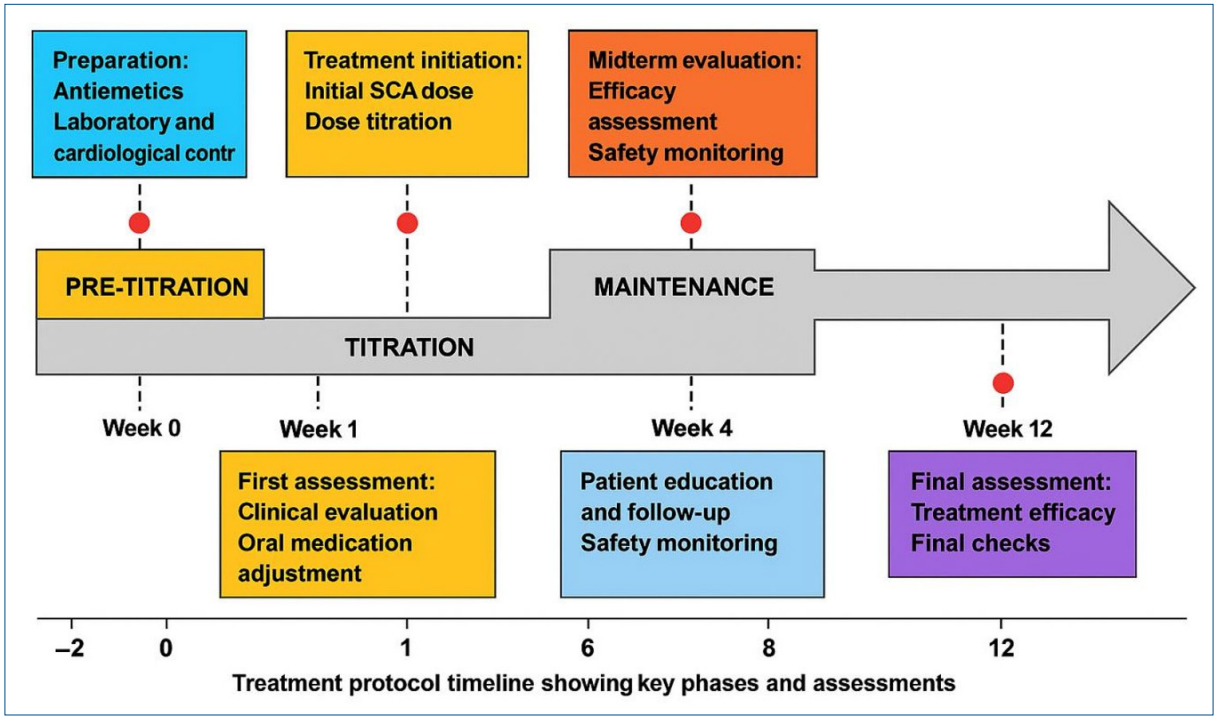

Figure 2. Apomorphine treatment protocol timeline

diaries. Daily off time, on without dyskinesia, and on-dyskinesia durations were calculated over a 16±2 h waking period.

Non-motor assessments: Were conducted pre-treatment and at week 12, both overall and stratified by age (<45 years vs ≥45 years). Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA); depression via the Beck Depression Inventory (BDI); quality of life with the Parkinson's Disease Questionnaire (PDQ-8); and sleep quality with the Parkinson's Disease Sleep Scale (PDSS).

Validated Turkish versions of all scales were used, and the administration and scoring were conducted in accordance with standardized procedures reported in the literature.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26. The primary analyses used repeated-measures ANOVA with time as the within-subject factor to test pre-specified endpoints. Between-group effects by age were examined with mixed-design ANOVA including age group as the between-subject factor and time as the within-subject factor. With two time points, sphericity is trivially satisfied. For the secondary endpoints, for PDQ-8, BDI, MoCA, PDSS, multiplicity was controlled using the Benjamini-Hochberg procedure across these outcomes. Exploratory variables were summarised descriptively only and were not subjected to hypothesis testing. Distributional assumptions were checked on change-score/residuals via Shapiro-Wilk; where assumptions were questionable, Wilcoxon signed-rank tests were used as sensitivity analyses. Outcome data are presented as 'Mean (SD)' . Between-group differences were assessed using mixed-design ANOVA, with Bonferroni correction applied to control for Type I error due to multiple comparisons. Significance was set at $p < 0.05$; effect sizes (η^2) were reported. No imputation was performed; analyses used complete cases for each endpoint.

RESULTS

The mean (SD) age of the participants was 67.71 (9.53) years, with a mean age at PD onset of 59.09 (11.43) years and a mean disease duration of 8.86 (3.42) years (Table 1). Males comprised 57.14% of the sample, and 28.57% were categorized as YOPD. The polyneuropathy was the most frequent comorbidity (42.9%), followed by cerebrovascular disease (17.1%) and epilepsy (5.7%); single cases (2.9% each) were recorded for bipolar disorder, TIA, ankylosing spondylitis and diabetes, and one patient had end-stage renal disease (2.9%); (28.6%) had no comorbidity. A Mann-Whitney U test comparing patients with any comorbidity (n=25) versus those without (n=10) showed no significant difference ($p > 0.05$). In multivariable analysis adjusted for age, sex and disease duration, presence of any comorbidity was not independently associated with the primary outcome ($p > 0.05$). All participants used at least one levodopa-containing medication, and 94% were also receiving dopamine agonists and monoamine oxidase-B inhibitors. The median intermittent SC apomorphine dose was 3.0 mg/day (IQR: 7.5–9.0), a median administration duration of 11 h/day. The most frequent early adverse events were sedation (34.3%) predominantly mild but with moderate sedation in 5.7% of the cohort; local skin irritation at the injection site in 22.9%, all mild; orthostatic hypotension in 20.0% of whom 8.6% of the cohort experienced moderate events while the remainder were mild; and nausea/vomiting/dizziness in 14.3% all mild. Injection-site nodules were not observed, and no other prespecified early events occurred. Most adverse events were mild to moderate and managed with symptomatic measures or dose adjustment. No treatment-related serious adverse events were observed. No significant associations were found between treatment response and baseline disease duration or severity. Similarly, no interaction was observed between improvements in UPDRS-III and mH&Y scores across the treatment period.

Efficacy Analysis: Pharmacological Outcomes

Pharmacological treatment efficacy was assessed via changes in daily levodopa dosage and LEDD from baseline to week 12. Daily levodopa dose significantly decreased from 574.03 (180.90) mg/day at baseline to 419.91 (78.09) mg/day post-treatment ($p < 0.001$). Similarly, LEDD declined from 242.17 (115.58) mg/day to 170.57 (61.20) mg/day ($p < 0.001$), suggesting a notable levodopa-sparing effect of intermittent SC apomorphine therapy (Table 1).

Efficacy Analysis: Motor Outcomes

Motor function during the "on" phase was evaluated at baseline and week 12 using MDS-UPDRS Part III, MHYS, total hours of "on" time without

Table 1. Demographic characteristics of patients

Variable	Mean (SD)	Median	Min–Max	IQR	25th Pctl	75th Pctl
Age (years)	67.71 (9.53)	70.0	43–86	17.0	58.0	75.0
PD onset age (years)	59.09 (11.43)	62.0	37–77	23.0	45.0	68.0
Duration of PD (years)	8.86 (3.42)	8.0	2–15	5.0	6.0	11.0
Daily levodopa dose before apomorphine (mg)	574.03 (180.90)	532.0	299–1064	125.0	500.0	625.0
Change in oral levodopa dose (mg)	419.91 (78.09)	399.0	266–637	125.0	375.0	500.0
Levodopa dose reduction (mg)	155.49 (161.04)	125.0	0–665	100.0	38.0	138.0
Levodopa dose reduction (%)	22.71 (16.81)	25.0	0–62.5	25.5	6.9	32.4
Daily LEDD before apomorphine (mg)	242.17 (115.58)	175.0	100–550	75.0	175.0	250.0
Change in LEDD (mg)	170.57 (61.20)	138.0	100–400	37.0	138.0	175.0
LEDD reduction (mg)	68.74 (62.24)	37.0	0–300	38.0	37.0	75.0
LEDD reduction (%)	25.01 (14.76)	21.2	0–56.3	16.3	21.2	37.5
Apomorphine usage period (times/day)	2.86 (1.03)	3.0	0–5	10.0	3.0	3.0
Apomorphine usage period (hours/day)	10.67 (3.06)	11.0	8–14	11.0	8.0	–
Daily apomorphine dosage (mg)	11.50 (11.75)	3.0	2–63	0.0	7.5	9.0

PD: Parkinson's disease; SD: standard devition; IQR: interquartile range; Pctl: percentile; LEDD: Levodopa equivalent daily dose.

Table 2. Correlative efficacy analysis of apomorphine treatment in terms of motor features

Variable	Mean (SD)	Median	Min- Max	IQR	25th Pctl	75th Pctl
MDS-UPDRS Part III 'On' (before apomorphine)	45.71 (11.93)	46.0	21–66	15.0	38.0	53.0
MDS-UPDRS Part III 'On' (after apomorphine)	29.86 (12.24)	30.0	0–56	17.0	21.0	38.0
mH&Y scale (before apomorphine)	2.97 (0.70)	3.0	2–4	0.5	2.5	3.0
mH&Y scale (after apomorphine)	1.89 (0.71)	2.0	1–3	1.0	1.0	2.0
'Off' time (h/day, before apomorphine)	5.60 (1.65)	6.0	2–10	2.0	4.0	6.0
'Off' time (h/day, after apomorphine)	2.26 (0.95)	2.0	0–4	1.0	2.0	3.0
'Off' time reduction (hours)	3.23 (1.35)	3.0	1–7	2.0	2.0	4.0
'Off' time reduction (%)	56.86 (16.88)	60.0	0–88	16.0	50.0	66.0
'On' time without dyskinesia (before apomorphine)	10.34 (1.76)	10.0	6–14	2.0	10.0	12.0
'On' time without dyskinesia (after apomorphine)	13.89 (0.93)	14.0	12–16	1.0	13.0	14.0
Increase in 'on' time (hours)	3.49 (1.50)	3.0	1–8	1.0	3.0	4.0
Increase in 'on' time (%)	22.79 (12.41)	17.0	8–58	15.0	14.0	29.0
'On' -dyskinesia time (before apomorphine)	4.23 (1.90)	4.0	2–8	3.0	3.0	6.0
'On' -dyskinesia time (after apomorphine)	1.86 (1.35)	2.0	0–4	3.0	0.0	3.0
Reduction in dyskinesia time (hours)	2.57 (1.46)	3.0	0–6	2.0	2.0	4.0
Reduction in dyskinesia time (%)	61.37 (31.11)	62.5	0–100	50.0	50.0	100.0

SD: standard deviation; IQR: interquartile range; mH&Y: modified Hoehn and Yahr; UPDRS: unified Parkinson's disease rating scale. All durations refer to a 16±2 hour waking day; Pctl: Percentile

Table 3. Correlative treatment efficacy analysis of apomorphine in terms of non-motor features

Variable	Mean (SD)	Median	Min-Max	IQR	25th Pctl	75th Pctl
PDQ-8 score (before apomorphine)	22.80 (5.60)	23.0	12–32	9.0	17.0	26.0
PDQ-8 score (after apomorphine)	17.54 (5.84)	18.0	8–32	6.0	16.0	22.0
BDI score (before apomorphine)	23.03 (5.70)	24.0	12–34	10.0	18.0	28.0
BDI score (after apomorphine)	18.09 (4.87)	18.0	8–28	8.0	14.0	22.0
PDSS score (before apomorphine)	65.31 (33.12)	65.0	30–135	52.0	38.0	90.0
PDSS score (after apomorphine)	60.60 (31.91)	61.0	15–140	40.0	35.0	75.0
MoCA score (before apomorphine)	15.74 (5.51)	16.0	8–25	10.0	11.0	21.0
MoCA score (after apomorphine)	18.03 (6.05)	18.0	8–28	11.0	13.0	24.0

PDQ-8: Parkinson's disease questionnaire-8; BDI: Beck depression inventory; PDSS: Parkinson's disease sleep scale; MoCA: Montreal cognitive assessment; SD: standard deviation; IQR: interquartile range; Pctl: percentile.

dyskinesia, and durations of "off" and "on-dyskinesia" periods. Mean MDS-UPDRS Part III scores improved from 45.71 (11.93) at baseline to 29.86 (12.24) at week 12 (p <0.001), while mH&Y scores decreased from 2.97 (0.70) to 1.89 (0.71) (p <0.001). "On" time without dyskinesia increased from 10.34 (1.76) hours/day to 13.89 (0.93) hours/day (p <0.001). Correspondingly, "off" time reduced from 5.60 (1.65) to 2.26 (0.95) hours/day (p <0.001), and "on-dyskinesia" time decreased from 4.23 (1.90) to 1.86 (1.35) hours/day (p <0.001). These changes indicate substantial motor benefit from intermittent SC "apomorphine treatment (Table 2).

Efficacy Analysis: Non-Motor Outcomes

Non-motor symptom (NMS) scores also showed statistically significant improvements following treatment (Table 3). MoCA scores increased from 15.74 (5.51) to 18.03 (6.05), reflecting improved cognitive function (p <0.001). Beck depression inventory scores decreased from 23.03 (5.70) to 18.09 (4.87), indicating alleviation in depressive symptoms (p<0.001). PDQ-8 scores improved from 22.80 (5.60) to 17.54 (5.84), showing enhanced quality of life (p <0.001). However, PDSS scores decreased slightly from 65.31 (33.12) to 60.60 (31.91), which was not statistically significant (p=0.433), suggesting limited effect on sleep quality.

Age-Stratified Analysis: Mixed Model Approach

Mixed-design ANOVA was used to examine treatment effects across age groups (<45 vs. ≥45 years). Within the YOPD subgroup, PDQ-8 and BDI scores significantly decreased [F (1,33)=388.83, p <0.001; F (1,33)=442.49, p <0.001, respectively], while MoCA scores significantly increased [F (1,33)=269.19, p <0.001] (Fig. 3). Between-group comparisons revealed no significant interaction effects (p >0.05), suggesting that treatment efficacy in non-motor domains was not significantly influenced by age at onset. These subgroup findings were consistent with the overall cohort analysis.

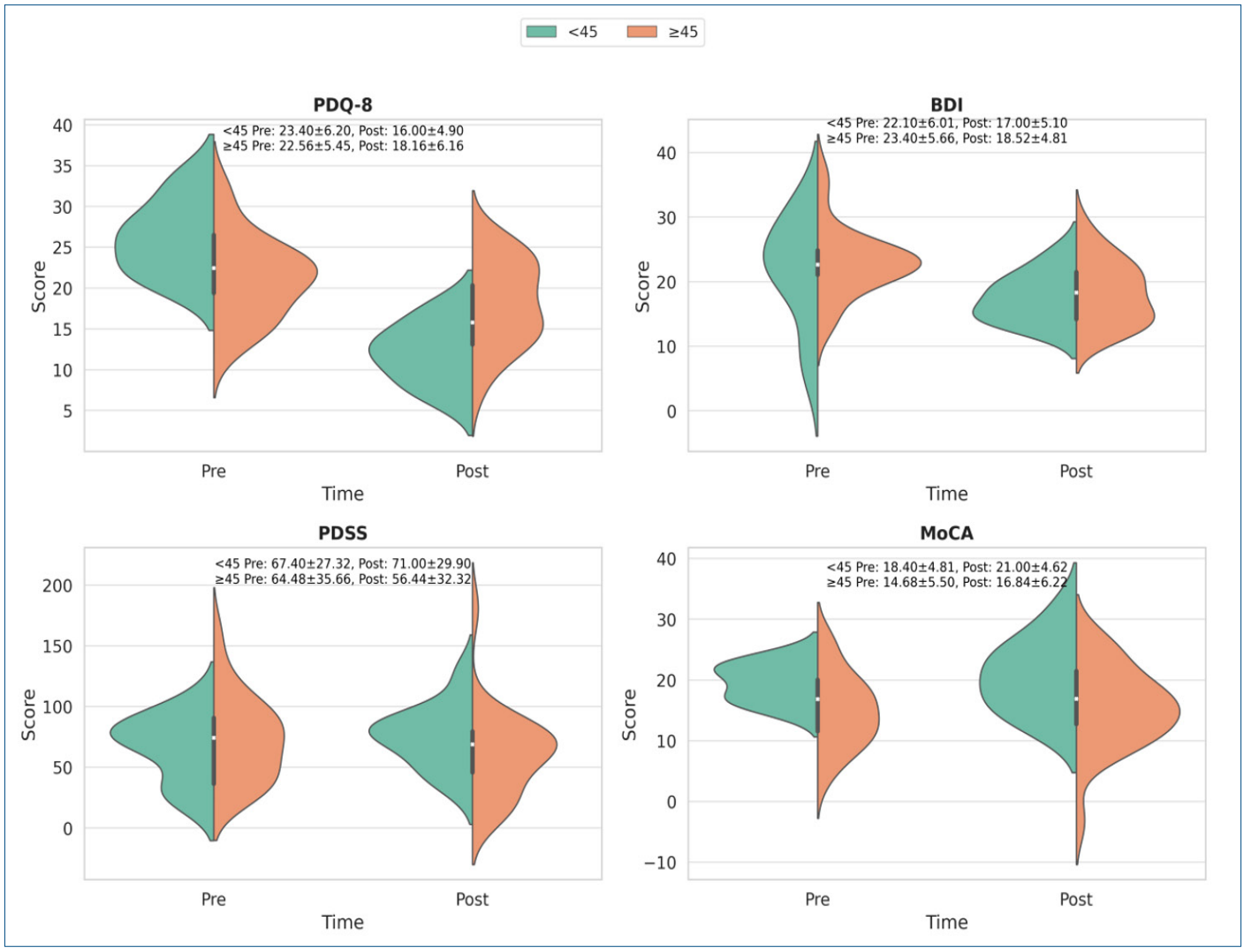

Figure 3. Age-stratified distributions of pre- and post-treatment scores for PDQ-8, BDI, PDSS and MoCA after 12-week intermittent apomorphine (SCA) administration in Parkinson's disease patients. For visualization, violin-like kernel density estimates are shown for each subgroup and timepoint with overlaid boxplots indicating median and interquartile range; small text above each violin reports the simulated group mean (m) and sample standard deviation (SD) computed from subject-level data simulated to match the reported group means and SDs. Solid violins/boxes correspond to patients with age at onset <45 years and dashed/alternate-position violins correspond to patients with age at onset ≥45 years.

DISCUSSION

In this prospective cohort study, intermittent SC apomorphine was associated with a significant decrease in MDS-UPDRS Part III scores, daily "off" time, and an increase in dyskinesia-free "on" time. Additionally, clinically significant improvements were observed in the MoCA, BDI, and PDQ-8, whereas no significant changes were observed in sleep measurements. The absence of an age × time interaction in the pre-specified age-subgroup analyses indicated that short-term responses were not significantly modulated by chronological age. Our study provided a prospective cohort with intermittent form not only in late-onset but also in early-onset patients, including multidimensional non-motor aspects. This represents one of the first prospective datasets suggesting that intermittent SC apomorphine may be an effective option.

In this study, the reduction in orally administered levodopa, coupled with a more continuous dopaminergic stimulation, also appeared to contribute to a decrease in dyskinesia episodes. In our patient cohort, "on" periods accompanied by dyskinesia were noticeably shortened. This improvement may be attributable to the prevention of high peak levodopa concentrations and the more stable dopaminergic tone achieved through intermittent apomorphine. Similarly, a study conducted in advanced stage PD patients reported that a three-month continuous SC apomorphine infusion resulted in an average reduction of approximately 200 mg in daily levodopa dose and a decrease of around three hours in daily "off" time (18). In a prospective observational study, the use of CSAI over a 12-month period led to a 51% reduction in daily "off" time and a 29% decrease in levodopa dosage (19). These findings collectively indicate a trend suggesting that long-term apomorphine treatment may contribute to the stabilization of dopaminergic tone.

Beyond motor improvements, apomorphine therapy has also been associated with favorable results in certain non-motor domains. Notably, significant enhancements in cognitive performance, mood and quality of life were observed. These outcomes may suggest that improved control of motor fluctuations exerts secondary benefits on cognitive and emotional well-being. The observed modest improvement in MoCA scores following initiation of intermittent apomorphine is most plausibly attributable to one of three, non-mutually exclusive mechanisms. First, indirect benefit: stabilisation of motor fluctuations reduces intercurrent fatigue, anxiety and attentional load, which can transiently improve performance (7). Second, direct pharmacological modulation: dopaminergic agents can

acutely modulate fronto-striatal networks that subserve working memory and processing speed, and short-term receptor occupancy changes may produce measurable improvements on global cognitive screening tools (12; 20). Third, the limited follow-up period increases the probability that small score changes reflect measurement variance rather than durable cognitive gain. We therefore recommend extended neuropsychological batteries with alternate forms, and longer follow-up intervals to determine the persistence and domain-specificity of cognitive effects (21). In line with previous literature, apomorphine infusion has not demonstrated any significant adverse effects on cognitive or behavioral function (22); on the contrary, important improvements in mood including depression and anxiety and apathy have been reported in some patients (23). On the other hand, our study did not show a significant change in PDSS scores, which assess sleep quality. This observation is consistent with the daytime-only administration of apomorphine in our protocol, which does not directly target nocturnal symptoms. Indeed, a controlled study, night-time apomorphine infusion significantly alleviated insomnia and improved PDSS scores in PD patients (24). The existing literature is insufficient for day-time application and the sleep quality quantification in this respect.

Our age group analyses demonstrated that cognitive, affective, and quality of life outcomes in YOPD cases were clinically comparable to those observed in late-onset cases. Prior observational and cohort reports from Spain and other centres have demonstrated that chronological age alone should not be the sole criterion for excluding patients from CSAI when individuals are appropriately selected and monitored (25,26). Crucially, our study asks a distinct, complementary question. Rather than examining long-term pump-delivered CSAI, we prospectively assessed the short-term impact of intermittent SC apomorphine administered via autoinjector, using pre-specified, diary-based, hour-by-hour motor state quantification, together with targeted non-motor outcome measures. By doing so, we extend the clinical principle that chronological age should not be an automatic exclusion criterion, showing that this principle applies not only to continuous infusion but also to intermittent injection strategies and to early non-motor benefits measured in routine clinical practice.

Apomorphine is an effective rescue therapy in the management of PD, but various mild side effects, such as nausea, vomiting, sedation, and local skin reactions, as well as serious side effects, such as severe hypotension with syncope, QTc prolongation, and cardiac arrhythmias, and in rare cases, respiratory depression and death, have been described (27,28). The early side effects observed in our study, such as sedation, local skin irritation, and orthostatic hypotension, were consistent with this common profile described in the literature, and no serious side effects were observed. In patients with multiple comorbidities, it should be preferred as a device-assisted treatment based on the benefit-to-risk ratio.

While the results are encouraging, several limitations must be acknowledged. The relatively short follow-up duration limit the ability to draw definitive conclusions regarding the long-term efficacy and cognitive outcomes of apomorphine. Part of the observed MoCA improvement may stem from retest effects or indirect benefits mediated by improved motor performance, rather than a direct pharmacological impact. Moreover, the relatively small sample size and heterogeneity in disease characteristics constrain the generalizability of the findings.

As a result, this study systematically evaluated the short-term effects of the injection method using hourly diary records, motor state quantification, and targeted early cognitive/mood measures. Our findings provide a pioneering cohort study supporting the notion that age alone should not be used as an exclusionary criterion for apomorphine use and highlight the need for a multidimensional assessment of comorbidity profile, baseline cognition/function, autonomic/cardiac risk, and patient preferences in selecting appropriate patients. In conclusion, an intermittent injection strategy has the potential to contribute to early non-motor outcomes beyond motor findings. This hypothesis requires validation in long-term, age-stratified, randomized trials and comprehensive geriatric assessments.

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