RESEARCH ARTICLE

Association of Adjunctive Pramipexole with Motor Performance, Sleep, and Behavioral Symptoms in Parkinson's Disease: A Prospective Cohort Study

Lailoma Shabir[1], Naeem Amjad[2], Isham Saleem Mughal[3], Abdul Mudabbir Rehan[4], Mudassar Ijaz[5], Saif ur Rehman[6]

[1]*Trainee Medical Officer. Department of Psychiatry. Mercy Teaching Hospital. Peshawar. Email ID: shabirlailoma@gmail.com*

[2]*Associate Professor. Department of Psychiatry and Behavioural Sciences. Shahida Islam Medical college. Lodhran. Email ID: drnaeemamjad@gmail.com*

[3]*Assistant Professor. Pharmacology Department. Fatima Jinnah Institute of Dental Sciences. Lahore. Email ID: drishamsaleem@gmail.com*

[4]*Associate Professor. Pharmacology Department. Postgraduate Medical Institute. Ameer-ud-Din Medical College. Lahore. Email ID: abdulmudabbir@yahoo.com*

[5]*NCHD. Midwest Mental Health Services. Ireland. Email ID: Madisrdar77@gmail.com*

[6]*Assistant Professor. Department of Behavioral Sciences. CMH Multan Institute of Medical Sciences. Multan. Email ID: nakhshab@yahoo.com*

***Corresponding Author:** Isham Saleem Mughal. Assistant Professor. Pharmacology Department. Fatima Jinnah Institute of Dental Sciences. Lahore. Email ID: drishamsaleem@gmail.com*

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Abstract

Background: Parkinson's disease affects movement, sleep and emotional well-being, and the dopamine agonists used to treat it carry behavioral and sedative risks.

Objective: To compare motor, sleep and behavioral outcomes of adjunctive pramipexole with those of continued levodopa-based care.

Methods: This prospective comparative cohort enrolled 120 adults at three tertiary care hospitals in Punjab, Pakistan treatment followed clinical decisions. Motor examination, timed mobility, nighttime sleep, daytime sleepiness, depression, anxiety and apathy were assessed at baseline and 12 weeks. Analyses adjusted for baseline score and for demographic, treatment and hospital variables. Adverse events were recorded throughout follow-up.

Results: Week-12 data were available for 111 participants. Pramipexole was associated with a lower motor score than usual care (adjusted difference −4.01 points; 95% confidence interval −6.39 to −1.63; p=0.001). Nighttime sleep (−3.62) and depressive symptoms (−3.37) also favored pramipexole, and anxiety and apathy scores were lower. Daytime sleepiness was 1.51 points higher than with usual care. Somnolence occurred in 18.3% versus 5.0%, and impulse-control disorders in four versus no participants. No serious adverse events occurred.

Conclusion: Adjunctive pramipexole was associated with better motor performance, nighttime sleep and some behavioral symptoms, at the cost of more daytime sleepiness. Because treatment was not randomized, these associations do not establish causation. Individualized prescribing with behavioral surveillance is advisable; short follow-up and a modest sample limit conclusions about rare harms and sustained benefit.

Keywords: Parkinson disease, Pramipexole, Motor activity, Impulse control disorders.

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Introduction

Parkinson's disease places a growing burden on patients, families and health services, and population ageing is projected to raise the number of people affected substantially over the coming decades.[1] In one prospective cohort, nonmotor symptoms evolved across several domains, and a heavier initial symptom burden predicted faster motor progression.[2] Daily functioning therefore deserves attention alongside the neurological examination, particularly when a medicine has both motor and psychiatric effects.

Local data point the same way. A Peshawar study documented frequent sleep disturbance, constipation and depressive symptoms among patients with Parkinson's disease.[3] In Rawalpindi, more than half of the patients studied had poor sleep quality, which was associated with older age and longer illness duration.[4] A Karachi investigation also found a substantial burden of depression, although its clinic-based sample could not yield a population prevalence.[5] A brief motor assessment alone can therefore miss clinically important problems.

Depression, anxiety and apathy each predict worsening quality of life over time, which makes them natural outcomes for joint psychiatric and neurological care.[6] In early disease, apathy accompanies a greater nonmotor burden and poorer health-related quality of life, so it merits assessment separately from depression.[7] Sleep needs similar care in definition. Systematic interviews and polysomnography reveal several overlapping sleep disorders even in early Parkinson's disease,[8] and excessive daytime sleepiness is linked longitudinally with cognitive, autonomic and psychiatric difficulties rather than simply reflecting poor nighttime rest.[9] Measuring nighttime disturbance and daytime alertness separately gives a more faithful picture of treatment response.

Wearable devices can relate activity and sleep measures to nonmotor impairment, but their limited predictive performance shows that technology has not yet replaced careful clinical assessment.[10] Imaging work has linked declining striatal dopamine transporter binding with apathy and anhedonia, supporting a dopaminergic contribution but not a treatment effect.[11] Clinical guidance favors levodopa for most patients who need initial motor treatment and advises careful selection and monitoring when a dopamine agonist is considered.[12] A recent pramipexole-containing trial showed that motor benefit and daytime sleepiness can both vary with the intensity of dopaminergic treatment, so the two outcomes need to be evaluated together.[13]

Behavioral safety matters to psychiatric and pharmacology teams alike. A multicenter cohort linked pramipexole exposure with impulse-control and related behavioral disorders, with additional risk tied to younger onset and psychiatric history.[14] Better mood or motivation cannot, therefore, be read as improvement in every behavioral domain. This study compared twelve-week changes in motor performance, nighttime sleep, daytime sleepiness and selected behavioral symptoms between patients receiving adjunctive pramipexole and those continuing levodopa-based care. A central question was whether better movement and rest came at the cost of alertness or new behavioral problems.

Materials and Methods

This prospective comparative cohort study was conducted from July 2025 to June 2026. Neurology and psychiatry services recruited consecutive patients and pharmacology investigators reviewed medication exposure and adverse events. Each participant was followed for twelve weeks. The ethics committee of each hospital approved the protocol and all participants gave written informed consent.

Eligible patients were aged 40–70 years, had clinically established idiopathic Parkinson's disease at modified Hoehn–Yahr stage 1.5–3, and had persistent motor difficulty despite at least four weeks of stable levodopa treatment. A neurologist confirmed the diagnosis using the Movement Disorder Society clinical diagnostic criteria. Exclusion criteria were atypical or secondary parkinsonism, dementia, active psychosis, previous impulse-control disorder, Epworth Sleepiness Scale (ESS) score above 10, estimated glomerular filtration rate below 60 mL/min/1.73 m², unstable medical illness and dopamine agonist exposure within eight weeks. Patients needing urgent psychiatric care were referred for treatment rather than enrolled.

The treating neurologist chose therapy independently of study participation. The exposure group received immediate-release pramipexole added to levodopa; the comparison group continued levodopa-based care without a dopamine agonist. Treatment was not randomized, and neither participants nor assessors were blinded. Pramipexole was started at 0.125 mg three times daily (expressed as the dihydrochloride monohydrate salt) and titrated no faster than weekly according to response and tolerability, usually to 1.5 mg/day and never above the study ceiling of 2.25 mg/day. Levodopa and psychiatric medicines were kept stable where clinically feasible, and necessary changes were documented. Adherence was checked through medication reconciliation and caregiver questioning, without electronic monitoring.

The sample size assumed a 4.5-point between-group difference in motor change, a standard deviation of eight points, 80% power and a two-sided alpha of 0.05, giving 50 evaluable participants per group. Allowing for 10% attrition raised the target to 56 per group, and 120 participants were ultimately enrolled. The calculation covered only the primary motor outcome and did not provide adequate power for uncommon adverse events.

Assessments took place at baseline and week 12, with telephone contacts during titration to check tolerability. The primary endpoint was the week-12 Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor examination score, adjusted for baseline. Motor examinations were performed in the usual ON state, approximately 60–90 minutes after a levodopa dose, at similar times on both visits. Timed Up and Go testing used the same chair and three-meter walkway, and the mean of two trials was recorded. Secondary instruments and score directions are listed in Table 1. Bilingual clinicians administered the questionnaires, giving consistent Urdu

explanations when needed; this approach has not been formally validated locally.

Table 1. Outcome assessment and interpretation

Domain	Instrument	Range and interpretation
Motor impairment	MDS-UPDRS III	0–132; higher indicates worse impairment
Functional mobility	Timed Up and Go	Seconds; longer indicates slower mobility
Nighttime sleep	PDSS-2	0–60; higher indicates worse disturbance
Daytime sleepiness	ESS	0–24; higher indicates greater sleepiness
Depressive symptoms	HAM-D-17	0–52; higher indicates greater severity
Anxiety symptoms	HAM-A	0–56; higher indicates greater severity
Apathy	AES clinician version	18–72; higher indicates greater apathy
Impulse-control behavior	QUIP short screen and interview	Positive screens require clinical confirmation

MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Scale part III; PDSS-2, Parkinson's Disease Sleep Scale, second version; ESS, Epworth Sleepiness Scale; HAM-D-17, 17-item Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; AES, Apathy Evaluation Scale; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease.

Psychiatrists evaluated every positive behavioral screen through patient and caregiver interviews. Safety surveillance covered nausea, somnolence, postural symptoms, hallucinations, dyskinesia and new impulse-control disorders. Stopping medication did not end follow-up. Participants who reported sudden sleep episodes received driving precautions and clinical review, while treatment decisions remained with the treating clinician.

Analyses were performed in Python using NumPy, SciPy and statsmodels. Data are summarized as mean ± standard deviation or n (%). Week-12 outcomes were compared using separate analyses of covariance adjusted for the corresponding baseline score, age, sex, disease duration, baseline levodopa dose and recruiting hospital (two indicator variables). Covariates were prespecified. Confidence intervals (95%) used HC3 robust standard errors. The primary analysis used complete follow-up records, and a sensitivity analysis carried baseline motor scores forward for missing week-12 observations. Holm correction was applied to the six secondary continuous outcomes. Safety comparisons used Fisher's exact test and were exploratory. Two-sided $p<0.05$ defined statistical significance. Behavioral scale scores were analyzed as continuous measures, not as individual diagnoses.

Results

Of 154 patients screened, 34 were excluded: 18 did not meet other eligibility criteria, eight had recent dopamine agonist exposure, five declined and three needed immediate treatment for another condition. Sixty patients received pramipexole and 60 received usual care. Week-12 assessments were available for 55 and 56 participants, respectively; the nine who could not return remained reachable for safety contacts.

Baseline characteristics are shown in Table 2. The pramipexole group had longer disease duration, higher levodopa doses and a larger proportion of men. Because treatment was not randomly assigned, these differences required adjustment; similar motor scores alone do not make the groups comparable.

Table 2. Baseline characteristics of the enrolled cohort

Characteristic	Pramipexole n=60	Usual care n=60
Age, years	60.3 ± 6.0	60.3 ± 7.0
Men, n (%)	46 (76.7)	38 (63.3)
Disease duration, years	5.8 ± 2.2	5.0 ± 1.8
Levodopa, mg/day	452.5 ± 109.9	414.2 ± 112.0
Modified Hoehn–Yahr stage, median (IQR)	2.0 (2.0–2.5)	2.0 (2.0–2.5)
MDS-UPDRS III	34.9 ± 7.1	34.0 ± 6.2
PDSS-2	24.5 ± 5.4	23.6 ± 5.9
HAM-D-17	14.6 ± 4.3	13.3 ± 4.1

Values are mean ± standard deviation unless stated otherwise. IQR, interquartile range. Baseline summaries include all 120 participants.

Adjusted motor and mobility outcomes favored pramipexole (Table 3), with a primary motor difference of −4.01 points. When baseline scores were carried forward for missing

motor observations, the difference narrowed to −3.64 points (95% confidence interval −5.88 to −1.40; p=0.002). The direction was unchanged, although this approach cannot remove bias arising from missing follow-up.

Table 3. Motor and mobility outcomes at twelve weeks

Outcome	Pramipexole baseline → week 12	Usual care baseline → week 12	Adjusted difference (95% CI)	p
MDS-UPDRS III	34.5 ± 7.0 → 27.6 ± 9.3	34.2 ± 6.3 → 31.3 ± 7.8	−4.01 (−6.39 to −1.63)	0.001
Timed Up and Go, seconds	15.3 ± 3.1 → 13.6 ± 3.3	14.7 ± 3.1 → 14.2 ± 3.4	−1.20 (−1.93 to −0.46)	0.002

Complete cases: 55 and 56. Values are mean ± standard deviation. Differences compare pramipexole with usual care after adjustment for baseline score and covariates; negative values favor pramipexole.

Nighttime disturbance improved, but daytime sleepiness increased (Table 4), so the sleep findings cannot be read as a uniform benefit. Mean ESS stayed below the excessive-sleepiness threshold, but averages can hide clinically important sleepiness in individuals.

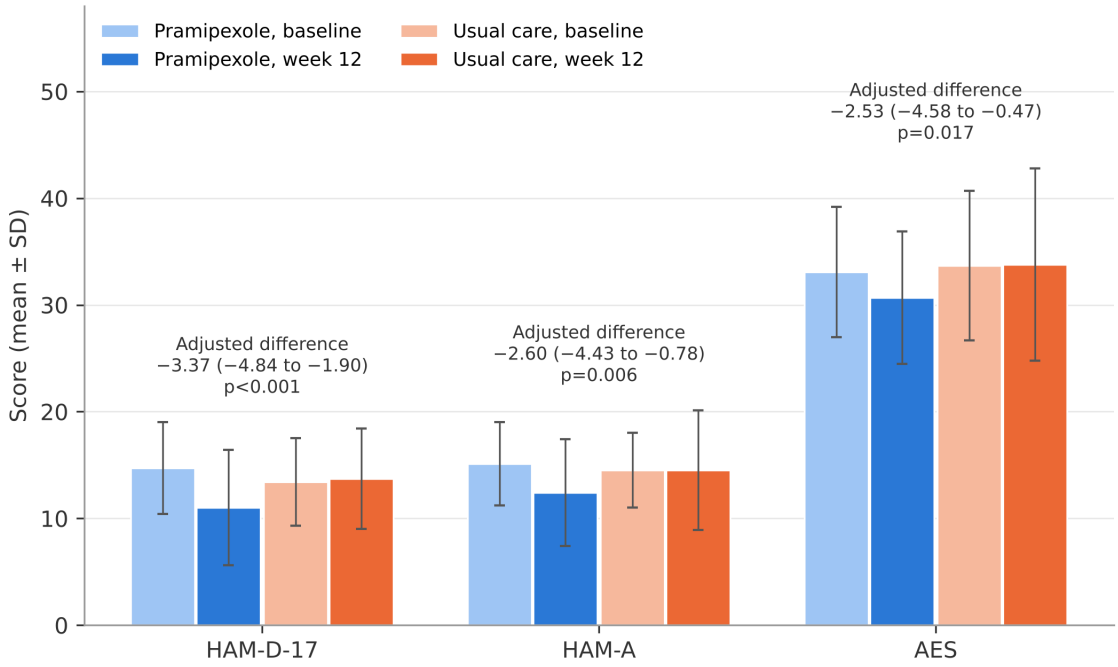
Table 4. Nighttime sleep and daytime sleepiness

Outcome	Pramipexole baseline → week 12	Usual care baseline → week 12	Adjusted difference (95% CI)	p
PDSS-2	24.5 ± 5.4 → 19.6 ± 6.3	23.9 ± 5.9 → 22.7 ± 7.4	−3.62 (−5.78 to −1.46)	0.001
ESS	6.1 ± 2.1 → 7.5 ± 3.2	5.6 ± 1.9 → 5.6 ± 2.8	1.51 (0.57 to 2.46)	0.002

Complete cases: 55 and 56. Higher scores indicate worse symptoms. Negative PDSS-2 differences favor pramipexole; positive ESS differences indicate greater daytime sleepiness.

Depression, anxiety and apathy scores all favored pramipexole (Figure 1). These differences reflect lower symptom severity, not confirmed psychiatric remission, and the apathy estimate was smaller and less precise. After Holm correction, p values for all six secondary continuous outcomes remained below 0.05.

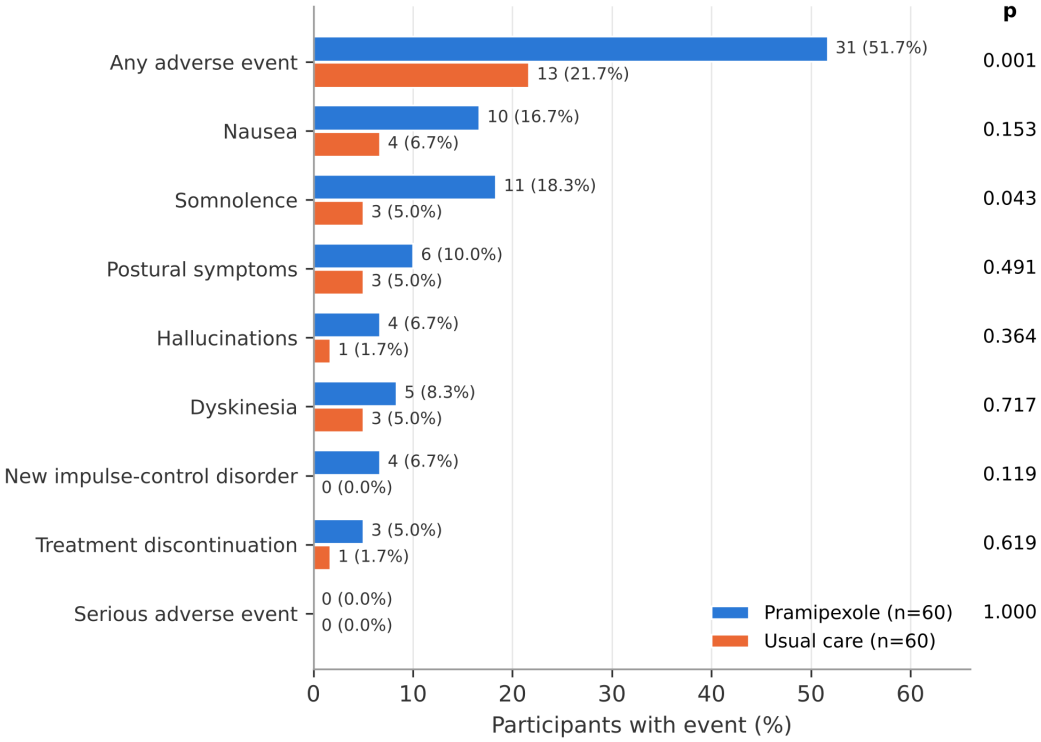
Figure 1. Emotional and motivational symptoms at baseline and week 12



Bars show means and error bars one standard deviation (complete cases: 55 and 56). Higher scores indicate worse symptoms. Adjusted differences (95% CI) compare pramipexole with usual care; p values are unadjusted.

Adverse events were more common with pramipexole (Figure 2), including four new impulse-control disorders. The nonsignificant comparison for these disorders does not demonstrate equivalent behavioral safety, because the events were rare. Few patients discontinued treatment, and no serious adverse events occurred during the twelve weeks.

Figure 2. Adverse events during follow-up



Bars show the percentage of each group (n=60) reporting the event; participants could report more than one event. Fisher's exact tests were exploratory and not adjusted for multiple comparisons.

Discussion

Adjunctive pramipexole was associated with better motor performance and nighttime sleep, but also with more daytime sleepiness, a clinically important split. The SUSTAIN trial found that sustained-release and immediate-release pramipexole both improved nocturnal symptoms, without showing either formulation to be superior for sleep disturbance.[15] Because it compared two active formulations and addressed a different clinical decision, its effect sizes cannot be compared directly with those reported here.

The reduction in depressive symptoms is consistent with an eight-week trial in which pramipexole and citalopram both lowered depression scores, with no clear difference between them.[16] An open-label trial likewise reported improvement with pramipexole, escitalopram and repetitive transcranial magnetic stimulation compared with routine treatment.[17] None of this makes pramipexole a substitute for psychiatric assessment. In another trial, adding Zishen Pingchan granules to pramipexole brought further gains in mood and sleep, but because both arms received pramipexole, the design could not isolate its antidepressant effect.[18]

The motor improvement fits with recent comparative evidence on pramipexole as a levodopa adjunct, although differences in comparators, baseline fluctuation and assessment timing rule out simple numerical comparison.[19] The ON-state examination used here captured performance at clinic visits and does not show a reduction in daily OFF time. Rising ESS scores need separate attention. A prospective biomarker cohort tied daytime sleepiness to broader disease burden and neuroaxonal injury, indicating causes beyond medication exposure,[20] and another longitudinal cohort linked sleep disorders with later impulsive-compulsive behaviors, which argues for monitoring sleep and behavior together.[21]

Better mood and less apathy do not rule out harmful behavioral effects. A large retrospective series documented impulse-control disorders even at relatively low pramipexole doses, so a low dose offers no firm assurance

of safety.[22] A cohort with early-onset disease also identified clinically important disorders among dopamine agonist users, although its younger population limits direct comparison with this sample.[23] Pharmacokinetic work found no correlation between pramipexole serum concentrations and impulse-control severity, reinforcing direct questioning of patients and caregivers.[24] The four events seen here are therefore clinically relevant despite the nonsignificant comparison.

Strengths of this study include its multicenter design across three tertiary hospitals, consistent ON-state examination timing at both visits, and separate assessment of nighttime sleep, daytime alertness and behavioral harm, with psychiatrists confirming behavioral events through patient and caregiver interviews. Prespecified covariate adjustment and a sensitivity analysis added rigor. The main limitations are nonrandom treatment selection, unblinded assessment and short follow-up. Remote rehabilitation also improves motor and nonmotor outcomes, so longer controlled studies should test pramipexole alongside such non-drug options.

Conclusion

Over twelve weeks, adjunctive pramipexole was associated with better motor performance, nighttime sleep and selected emotional and motivational symptoms. Greater daytime sleepiness and new impulse-control disorders offset part of this benefit, and nonrandom treatment selection rules out a causal conclusion. The findings support careful patient selection and repeated assessment of alertness and behavior alongside motor response.

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