

Original Article

Assessment of rasagiline as add-on therapy to levodopa for selected motor and non-motor symptoms in Parkinson's disease

Jingya Sun¹, Dapeng Tong¹, Shuoyan Zhou², Mingzhuo Wei¹, Ge Yu¹, Chen Liu¹, Xin Gao¹

¹School of Pharmacy, Heilongjiang University of Chinese Medicine, Harbin 150040, Heilongjiang, China;

²Department of Pulmonary Diseases, Second Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin 150001, Heilongjiang, China

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Abstract: Objectives: Motor fluctuations are a disabling complication in Parkinson's disease (PD) patients on long-term levodopa therapy. Rasagiline is a monoamine oxidase-B (MAO-B) inhibitor. It is commonly used as an add-on treatment. This study evaluated the effects of rasagiline on motor and non-motor symptoms. We also examined its effects on quality of life and on serum inflammatory markers. Methods: This retrospective study enrolled 158 PD patients with motor fluctuations treated with levodopa at our medical facility from January 2022 to January 2025. Patients were categorized into a monotherapy group (levodopa only, n=88) and an add-on group (levodopa plus rasagiline 1 mg/day, n=70). Motor symptoms, non-motor symptoms, quality of life, and laboratory indicators were assessed at baseline and after 6 months. Adverse events were recorded. Results: After 6 months, the add-on group had significantly shorter daily off time ($P<0.001$) and greater daily on time ($P<0.001$). Notable improvements were also observed in the Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III ($P<0.001$) and Part II ($P<0.001$), as well as on the Hamilton Depression Rating Scale ($P=0.008$), Fatigue Severity Scale ($P=0.019$), Epworth Sleepiness Scale ($P=0.015$), and Parkinson's Disease Questionnaire-39 ($P=0.009$). Hamilton Anxiety Rating Scale scores did not differ significantly ($P=0.119$). Serum neutrophil-to-lymphocyte (NLR) ratio, C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) were all significantly reduced ($P<0.001$). The overall adverse event rate was similar ($P=0.132$). Conclusions: In this retrospective observational study, add-on rasagiline therapy was associated with improvements in motor function, selected non-motor domains (depression, fatigue, and daytime sleepiness), quality of life, and reductions in peripheral inflammatory markers. The overall adverse event frequency was similar between treatment groups.

Keywords: Parkinson disease, levodopa, rasagiline, drug therapy, combination, motor symptoms, non-motor symptoms, quality of life

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative condition characterized by a deficiency of dopamine in the striatum, resulting in cardinal motor symptoms including bradykinesia, rigidity, resting tremor, and postural instability [1, 2]. Levodopa remains the most effective medication for controlling the symptoms of PD. However, as the disease progresses and treatment is prolonged, the therapeutic window narrows, and disabling motor fluctuations occur [3]. The most common is the "wearing-off" phenomenon, where the effect of the

medication diminishes before the next dose is taken, leading to an extended "off period" each day, severely impairing patient's functional independence and quality of life [4]. Therefore, finding ways to extend the duration of action of levodopa and stabilize the alternation between the active and off periods has become a central focus in the treatment of advanced PD [5].

Rasagiline is a selective, irreversible monoamine oxidase B (MAO-B) inhibitor, which inhibits central dopamine breakdown, thereby increasing synaptic dopamine levels [6]. By prolonging the half-life of endogenous and exoge-

nous (levodopa-derived) dopamine, rasagiline provides patients with more sustained dopaminergic stimulation [7]. Multiple randomized controlled trials have demonstrated that taking rasagiline once daily as an adjunctive treatment to levodopa significantly reduces the “off” periods in patients with motor fluctuations, while also improving their motor function. This evidence positions rasagiline as a first-line adjunctive therapy for the treatment of PD motor fluctuations [8].

Apart from classic motor symptoms, PD is increasingly recognized as a complex disorder characterized by multiple non-motor symptoms. Depression, anxiety, fatigue, and excessive daytime sleepiness are among the most common and distressing non-motor features. They often precede motor fluctuations and can independently worsen disability [9, 10]. These symptoms often correlate with each other and with motor impairments, making them strong predictors of poor health-related quality of life [11]. Given the involvement of dopaminergic pathways in mood regulation, arousal, and motivation, optimizing dopaminergic tone with rasagiline may theoretically improve certain non-motor domains. However, the clinical data on rasagiline's effects in non-motor areas remains limited, and the findings have been inconsistent. While some studies suggest modest benefits for fatigue and mood, others indicate no significant difference compared to placebo. Therefore, the overall impact of this medication on non-motor aspects has not been fully elucidated [12].

Furthermore, mounting evidence suggests a link between chronic low-grade systemic inflammation and the onset and progression of PD [13, 14]. MAO-B inhibitors such as rasagiline have demonstrated neuroprotective and anti-inflammatory effects in preclinical studies, primarily through inhibition of oxidative stress and glial activation [15]. However, it remains unclear whether these properties translate into clinically meaningful reductions in systemic inflammatory markers in patients receiving levodopa therapy.

Given the multidimensional burden of PD, an ideal treatment strategy should address both motor and non-motor aspects that substantially impair patients' daily functioning. However, real-world studies simultaneously evaluat-

ing the effects of rasagiline add-on therapy on validated motor scales, commonly burdensome non-motor domains, quality-of-life outcomes, and inflammatory biomarkers in a single cohort remain scarce. The current study sought to evaluate the effects of adjunctive rasagiline on motor symptoms, selected non-motor symptoms (depression, anxiety, fatigue, and daytime sleepiness), quality of life, and serum inflammatory markers in PD patients with motor fluctuations.

Materials and methods

Patient selection

A retrospective analysis was conducted on 158 PD patients with motor fluctuations who received levodopa treatment at the Second Affiliated Hospital of Heilongjiang University of Chinese Medicine between January 2022 and January 2025. The study protocol was reviewed and approved by the Institutional ethical Review Board (IRB) of the Second Affiliated Hospital of Heilongjiang University of Chinese Medicine. Because this was a retrospective chart-review study involving no direct patient contact, no additional interventions beyond standard clinical practice, and the use of fully anonymized data, the IRB granted a waiver of individual informed consent in accordance with the Declaration of Helsinki and applicable Chinese regulations for non-interventional retrospective research.

Inclusion criteria: ① Clinical diagnosis of idiopathic PD [16]; ② Aged 30 to 85 years, with no gender restrictions; ③ Presence of motor fluctuations (characterized by “wearing off phenomenon”), with a total daily “off” time of ≥ 2 hours (excluding morning akinesia); ④ Levodopa equivalent daily dose ≥ 300 mg/d and stable treatment for ≥ 8 weeks; ⑤ Hoehn-Yahr (H-Y) stage of 2 to 4 during “off” periods; ⑥ Complete medical records.

Exclusion criteria: ① Use of MAO-A inhibitors, MAO-B inhibitors, or catechol-O-methyltransferase inhibitors within the past 3 months; ② Parkinson's syndrome or multiple system atrophy caused by drugs, metabolic diseases, encephalitis, or basal ganglia diseases; ③ Co-existing severe hypertension, cardiovascular and cerebrovascular diseases, psychiatric disorders, epilepsy, severe hepatic or renal insuf-

iciency, or hematological diseases; ④ Moderate-to-severe cognitive impairment (defined as a documented clinical diagnosis of dementia and/or a Montreal Cognitive Assessment [MoCA] score <16/30 or Mini-Mental State Examination [MMSE] <20/30); ⑤ Severe motor disability corresponding to Hoehn-Yahr stage 5; ⑥ Pregnant or breastfeeding women; ⑦ Known allergy to the drug components or individuals with a history of allergies; ⑧ Use of vasodilators, central nervous system stimulants, analgesic anesthetics, etc., within the past month.

Depending on the treatment method, the 158 patients were divided into a monotherapy group (n=88) and an adjunctive therapy group (n=70). Patients in the monotherapy group received only levodopa, while those in the adjunctive therapy group received rasagiline as an add-on to levodopa treatment. This was a retrospective observational cohort study. Treatment allocation was not randomized; it was determined by routine clinical practice, based on physician judgment and shared decision-making with patients.

Treatment method

Patients in the monotherapy group continued their existing levodopa treatment regimen unchanged, continuing to take oral levodopa tablets (Approval No. H33021919, Ningbo Tianheng Pharmaceutical Co., Ltd., China). Patients in the adjunctive therapy group, while maintaining their original levodopa treatment regimen, additionally took oral rasagiline mesylate tablets (Approval No. H20213529, Qilu Pharmaceutical Co., Ltd., China) at a dose of 1 mg per day. Both groups were treated continuously for 6 months.

Data extraction

Data on motor and non-motor symptom scores, quality of life, serum inflammatory markers, and adverse reactions were extracted from the electronic medical record system at baseline and 6 months post-treatment. Primary outcomes were motor and non-motor symptoms scores. Secondary outcomes included quality of life, serum inflammatory markers, and adverse reactions. Given the retrospective design and the constraints of the electronic medical record system, non-motor symptoms were as-

sessed using a focused set of validated scales targeting four domains that are among the most prevalent, functionally disabling, and clinically actionable in PD patients with motor fluctuations [9-11]: depression, anxiety, fatigue, and daytime sleepiness. Other core non-motor domains-including cognitive function, autonomic dysfunction (e.g., constipation, orthostatic hypotension), sleep architecture, and hyposmia-were not systematically documented in the medical records at baseline or follow-up and therefore could not be evaluated in this study.

(1) On-Off Time: Data on daily "off" time and daily "on" time were collected. Daily off time was calculated as the sum of all 30-minute periods marked as "off" throughout the day, while daily on time was the sum of all 30-minute periods marked as "on" (including periods without dyskinesia and with varying degrees of dyskinesia).

(2) Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Part II assesses activities of daily living (ADL), covering speech, saliva secretion and swallowing, hand function, dressing, walking, turning in bed, and personal hygiene. This section yields a total score ranging from 0 to 52. Higher scores indicate worse daily living function. Part III evaluates motor symptoms, including speech and facial expressions, limb movements, rigidity, tremor, posture, and gait, with scores ranging from 0 to 132. Higher scores in this section indicate more severe motor symptoms (rigidity, bradykinesia, tremor). The Cronbach's α coefficient for MDS-UPDRS ranges from 0.79 to 0.93 [17].

(3) Depression and Anxiety: Depression and anxiety were assessed using the Hamilton Depression Rating Scale (HAMD-17) and Hamilton Anxiety Rating Scale (HAMA-14), respectively. Higher scores indicate more severe symptoms. The Cronbach's α coefficients are 0.77 and 0.893 for HAMD-17 and HAMA-14, respectively [18, 19].

(4) Fatigue and Daytime Sleepiness: The Fatigue Severity Scale (FSS) and the Epworth Sleepiness Scale (ESS) were used to assess the severity of fatigue and daytime sleepiness, respectively. Scores are positively correlated with symptom severity. The Cronbach's α coefficients are 0.960 and 0.84 for FSS and ESS, respectively [20, 21].

(5) Parkinson's Disease Quality of Life Questionnaire (PDQ-39): This questionnaire reflects the quality of life of PD patients over the past month, consisting of 39 questions scored based on frequency (0 = never, 4 = always). The final score is typically converted to an index ranging from 0 to 100, where higher scores indicate poorer quality of life (i.e., greater impact of the disease on life). The Cronbach's α coefficient for PDQ-39 ranges from 0.72 to 0.95 [22].

(6) Laboratory Indicators: White blood cell count (WBC), platelet count (PLT), neutrophil count (NEUT), and lymphocyte count (LYM) were measured using an automated hematology analyzer (XN-9000, Sysmex, Japan). The neutrophil-to-lymphocyte ratio (NLR) was computed as $NLR = NEUT / LYM$. Serum C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) levels were assessed using enzyme-linked immunosorbent assay (ELISA) kits (ab260058, ab178013, ab181421, Abcam, China). Fasting peripheral blood samples were collected between 7:00 and 9:00 AM after an overnight fast of at least 8 hours.

(7) Adverse Reactions: The occurrence of adverse reactions (headache, nausea, dry mouth, rash, dyskinesia, and others) during treatment was compared between the two groups.

Statistical analysis

Data analysis was performed using SPSS 29.0. Prior to analysis, all continuous variables were tested for normality using the Shapiro-Wilk test and for homogeneity of variances using Levene's test. For variables that satisfied both assumptions (normality and equal variances), data are expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), and intergroup differences were evaluated using independent samples t-tests. For variables violating either assumption, data are expressed as median (interquartile range, IQR), and intergroup comparisons were performed using the Mann-Whitney U test. Categorical variables are presented as frequencies [n (%)] and were compared between groups using the χ^2 test, or Fisher's exact test when any expected cell count was less than 5. A two-sided P value <0.05 was considered statistically significant.

Given the multiplicity of outcome indicators examined in this study (including motor symp-

toms, non-motor symptoms, quality of life, and inflammatory biomarkers), we applied the Benjamini-Hochberg false discovery rate (FDR) procedure to control the type I error rate across all comparisons of primary and secondary efficacy endpoints. The FDR was set at 0.05, and adjusted q -values were calculated for each comparison. Statistical significance was defined as adjusted $q < 0.05$ in addition to unadjusted $P < 0.05$. Missing data were not anticipated in this cohort because the study exclusively included patients with complete medical records per the enrollment criteria; consistent with this, no missing values were encountered for any primary or secondary outcome, and no imputation was performed.

Results

Basic characteristics

Baseline characteristics were comparable between the two groups (**Table 1**). No significant differences were observed in age ($P=0.186$), sex distribution ($P=0.833$), BMI ($P=0.570$), Parkinson's disease duration ($P=0.410$), levodopa equivalent dose ($P=0.711$), or Hoehn-Yahr stage distribution ($P=0.908$).

Motor symptoms

Baseline off time and on time were comparable between groups ($P=0.631$ and $P=0.392$, respectively). After the 6-month intervention, patients receiving adjunctive rasagiline experienced a significantly greater reduction in daily off time ($t=11.155$, $P<0.001$) and a significantly greater increase in daily on time ($t=5.659$, $P<0.001$) compared with those continuing levodopa alone (**Table 2**).

Similarly, baseline MDS-UPDRS Part II and Part III scores were comparable between groups ($P=0.814$ and $P=0.853$, respectively). Following treatment, the adjunctive therapy group showed significantly lower scores on both Part II ($t=3.685$, $P<0.001$) and Part III ($t=3.830$, $P<0.001$), indicating greater improvements in daily living activities and motor function (**Figure 1**).

Non-motor symptoms

Baseline HAMD-17 and HAMA-14 scores were similar between groups ($P=0.715$ and $P=0.556$, respectively). By the end of treatment, the

Table 1. Comparison of basic information between the two groups

Indicator	Monotherapy group (n=88)	Adjunctive therapy group (n=70)	t/χ ²	P
Age (years)	68.52 ± 5.98	69.83 ± 6.42	1.329	0.186
Sex [n (%)]			0.044	0.833
Male	53 (60.23%)	41 (58.57%)		
Female	35 (39.77%)	29 (41.43%)		
BMI (kg/m ²)	23.45 ± 2.91	23.18 ± 3.15	0.569	0.570
PD duration (years)	7.93 ± 3.38	7.51 ± 2.94	0.827	0.410
Levodopa equivalent dose (mg/d)	538.64 ± 92.33	544.29 ± 98.72	0.371	0.711
H-Y stage [n (%)]			0.193	0.908
2	24 (27.27%)	20 (28.57%)		
3	22 (25.00%)	19 (27.14%)		
4	42 (47.73%)	31 (44.29%)		

BMI, body mass index; PD, Parkinson's disease; H-Y, Hoehn-Yahr.

Table 2. Comparison of off time and on time between the two groups (h/d)

Indicator	Monotherapy group (n=88)	Adjuvant group (n=70)	t	P
Off time				
Before treatment	3.15 ± 0.78	3.21 ± 0.71	0.482	0.631
After treatment	2.82 ± 0.92	1.43 ± 0.65	11.155	<0.001*
On time				
Before treatment	11.28 ± 1.94	11.02 ± 1.78	0.858	0.392
After treatment	11.79 ± 2.05	13.56 ± 1.82	5.659	<0.001*

*, q<0.05.

adjunctive group had a significantly lower HAMD-17 score (t=2.706, P=0.008), whereas no significant between-group difference was observed for HAMA-14 scores (P=0.119, **Table 3**).

Concerning fatigue and daytime sleepiness, FSS and ESS scores were initially comparable (P=0.637 and P=0.408). After 6 months, the adjunctive therapy group exhibited significantly lower scores on both the FSS (t=2.365, P=0.019) and the ESS (t=2.472, P=0.015), reflecting meaningful reductions in fatigue and excessive daytime sleepiness (**Table 4**).

Quality of life

Baseline PDQ-39 scores were comparable between groups (P=0.920, **Figure 1**). At the post-treatment assessment, patients in the adjunctive group reported significantly greater improvement in quality of life (t=2.645, P=0.009).

Laboratory indicators

Baseline hematological parameters did not differ significantly between groups (all P>0.05). Following treatment, NLR was significantly lower in the adjunctive group than in the monotherapy group (P<0.001; **Table 5**).

Baseline inflammatory marker levels did not differ significantly between groups (all P>0.05). After treatment, CRP, IL-6, and TNF-α

were markedly lower in the adjunctive therapy group than in the monotherapy group (all P<0.001; **Table 6**).

Adverse reactions

The overall incidence of adverse events was similar between groups (P=0.132). Headache, nausea, dry mouth, rash, dyskinesia, and other events occurred at low frequencies and were similarly distributed between groups (**Table 7**).

Discussion

This study evaluated the multidimensional effects of adding rasagiline to ongoing levodopa therapy in PD patients with motor fluctuations. The findings indicate that adjunctive rasagiline was associated with greater improvements in motor and non-motor domains, quality of life, and systemic inflammatory markers, with a tolerability profile comparable to levodopa monotherapy.

Rasagiline add-on for Parkinson's disease

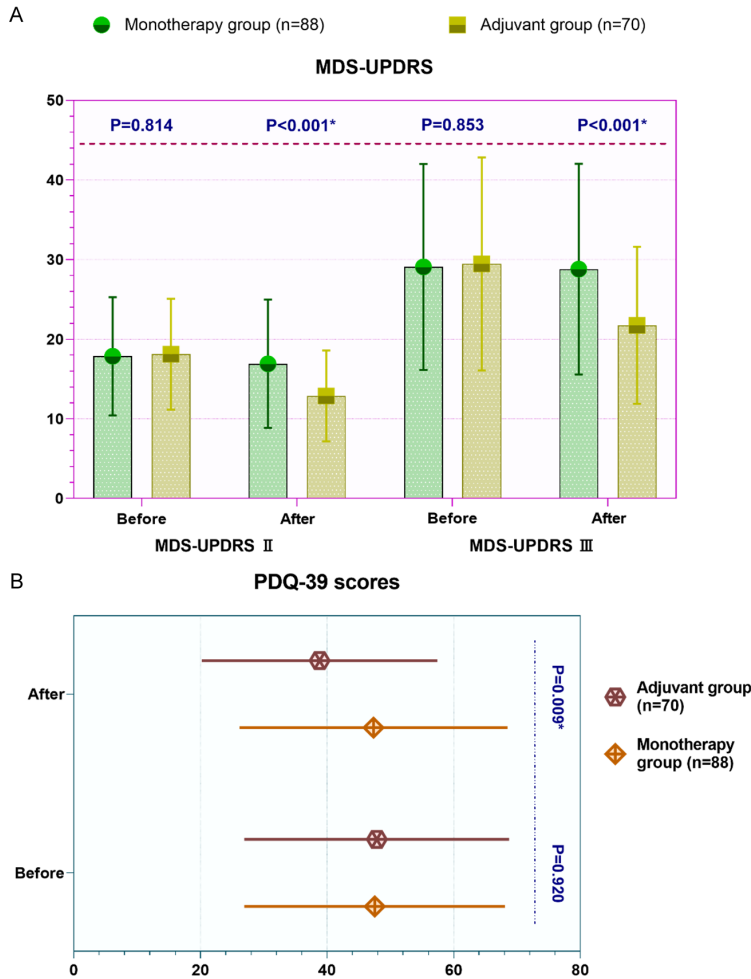


Figure 1. Comparison of MDS-UPDRS and PDQ-39 scores between the two groups (points). A. MDS-UPDRS; B. PDQ-39. MDS-UPDRS, Movement Disorder Society-Unified Parkinson's disease rating scale; PDQ-39, Parkinson's disease questionnaire-39; *, $q < 0.05$.

Table 3. Comparison of depression and anxiety scores between the two groups (points)

Indicator	Monotherapy group (n=88)	Adjuvant group (n=70)	t	P
HAMD-17				
Before treatment	9.42 ± 4.14	9.64 ± 3.28	0.365	0.715
After treatment	9.15 ± 3.92	7.82 ± 2.15	2.706	0.008*
HAMA-14				
Before treatment	8.43 ± 2.95	8.74 ± 3.61	0.590	0.556
After treatment	8.35 ± 3.08	7.67 ± 2.36	1.567	0.119*

HAMD-17, Hamilton depression scale-17; HAMA-14, Hamilton anxiety scale-14; *, $q < 0.05$.

Motor improvement was primarily reflected in reduced daily off time and increased on time. Additionally, MDS-UPDRS and Part II and Part III

scores decreased significantly. These changes align with the pharmacological action of rasagiline as a selective, irreversible MAO-B inhibitor [23]. Rasagiline reduces fluctuations in striatal dopamine availability by prolonging the synaptic presence of dopamine derived from both residual endogenous synthesis and exogenous levodopa. These fluctuations are the root cause of wearing-off phenomena. Thus, rasagiline provides more continuous dopaminergic stimulation, prolonging functional on time and improving motor performance quality [24]. Previous randomized trials, including PRESTO and LARGO, have demonstrated the motor benefits of daily administration of 1 mg rasagiline in reducing off time [25]. Now, our real-world observations further support these findings and demonstrate improvements in daily living activities, as reflected by MDS-UPDRS Part II [26].

In addition to motor function improvement, patients in the rasagiline group showed more pronounced reductions in selected non-motor symptoms. For example, after receiving the adjunctive treatment, the severity of depressive symptoms as assessed by the HAMD-17 scale decreased more significantly. Dopaminergic projections to the prefrontal cortex and limbic system are closely linked to emotional regulation, and MAO-B inhibition may enhance monoaminergic signaling in these circuits [6]. These findings are consistent with modest antidepressant effects, as partially supported by earlier studies [27], although some controlled studies have failed to show superiority over placebo. Patients also experi-

Table 4. Comparison of fatigue and sleepiness scores between the two groups (points)

Indicator	Monotherapy group (n=88)	Adjuvant group (n=70)	t	P
FSS				
Before treatment	4.92 ± 1.24	5.01 ± 1.18	0.473	0.637
After treatment	4.78 ± 1.31	4.35 ± 0.95	2.365	0.019*
ESS				
Before treatment	8.36 ± 2.42	8.69 ± 2.54	0.829	0.408
After treatment	8.15 ± 2.63	7.27 ± 1.85	2.472	0.015*

FSS, fatigue severity scale; ESS, Epworth sleepiness scale; *, q<0.05.

Table 5. Comparison of routine blood indicators between the two groups

Indicator	Monotherapy group (n=88)	Adjuvant group (n=70)	t	P
WBC (×10 ⁹ /L)				
Before treatment	6.48 ± 1.21	6.52 ± 1.18	0.186	0.853
After treatment	6.45 ± 1.19	6.13 ± 1.02	1.767	0.079
PLT (×10 ⁹ /L)				
Before treatment	227.35 ± 41.62	229.14 ± 43.05	0.264	0.792
After treatment	226.81 ± 40.97	218.67 ± 38.23	1.279	0.203
NLR				
Before treatment	3.23 ± 1.46	3.29 ± 1.52	0.258	0.797
After treatment	2.96 ± 1.04	1.62 ± 0.78	9.269	<0.001*

WBC, white blood cell count; PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; *, q<0.05.

Table 6. Comparison of inflammatory factors between the two groups

Indicator	Monotherapy group (n=88)	Adjuvant group (n=70)	t	P
CRP (mg/L)				
Before treatment	1.05 ± 0.52	1.08 ± 0.47	0.350	0.727
After treatment	0.97 ± 0.44	0.41 ± 0.25	10.033	<0.001*
IL-6 (pg/mL)				
Before treatment	2.87 ± 1.32	2.93 ± 1.28	0.279	0.781
After treatment	2.68 ± 1.18	1.72 ± 0.81	5.984	<0.001*
TNF-α (pg/mL)				
Before treatment	6.85 ± 2.51	6.91 ± 2.6	0.148	0.883
After treatment	6.62 ± 2.38	4.28 ± 1.85	6.982	<0.001*

CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; *, q<0.05.

enced greater improvements in fatigue and excessive daytime sleepiness, as reflected in lower FSS and ESS scores. Possible explanations include improved nocturnal motor function leading to more restorative sleep, en-

hanced dopaminergic transmission exerting direct arousal effects, or reduced systemic inflammation alleviating disease-related symptoms [28, 29]. Furthermore, the shorter duration of daily rest periods itself can reduce the physical burden associated with performing exercise tasks when mobility is impaired, thereby alleviating fatigue. Previous reports on rasagiline' effect on fatigue and sleepiness have been inconsistent, and our data add to the evidence that sustained MAO-B inhibition may provide clinically meaningful relief of these disabling non-motor features [30].

Improvement in quality of life, as quantified by the PDQ-39, serves as a patient-centered summary of the multidimensional benefits. Reductions in both motor and non-motor symptom severity likely converge to enhance daily functioning and overall well-being [31]. This aligns with LARGO trial analyses, where motor benefits of rasagiline translated into improved patient-reported quality of life [32].

A key finding was the marked reduction in serum inflammatory markers (NLR, CRP, IL-6, and TNF-α) in the adjunctive group. Elevated levels of these markers have been linked to faster motor decline and greater disability in PD [33]. Pre-clinical studies have demonstrated that rasagiline and its metabolite aminoindan can inhibit microglial activation, re-

duce pro-inflammatory cytokine production, and upregulate neurotrophic factors [34, 35]. The present observational data-showing reduced NLR and pro-inflammatory cytokines in the adjunctive group-are consistent with these

Table 7. Comparison of adverse reactions incidence between the two groups [n (%)]

Indicator	Monotherapy group (n=88)	Adjuvant group (n=70)	χ^2	P
Overall incidence rate	12 (13.64%)	16 (22.86%)	2.273	0.132
Headache	2 (2.27%)	3 (4.29%)		
Nausea	3 (3.41%)	4 (5.71%)		
Dry mouth	2 (2.27%)	4 (5.71%)		
Rash	2 (2.27%)	2 (2.86%)		
Dyskinesia	1 (1.14%)	1 (1.43%)		
Others	2 (2.27%)	2 (2.86%)		

preclinical findings and emerging clinical reports of MAO-B inhibition lowering peripheral inflammatory markers in PD [36]. However, this study was not designed to establish a mechanistic link between these inflammatory changes and clinical improvements. Correlation or mediation analyses between changes in inflammatory markers clinical scores were not performed. Confounding factors affecting peripheral inflammation (e.g., intercurrent infections, diurnal cortisol variation, concomitant anti-inflammatory agent use) were not systematically controlled in this retrospective review. Therefore, the anti-inflammatory findings should be interpreted as exploratory and hypothesis-generating, rather than as evidence of a mediating pathway. Whether peripheral anti-inflammatory effects contribute to rasagiline's symptomatic benefits requires prospective studies with standardized biosampling and formal mediation analyses. The similar incidence of adverse events between groups confirms the favorable safety profile of rasagiline added to levodopa.

Several important limitations of this study should be acknowledged. First, the non-randomized, retrospective design carries inherent risks of selection bias, prescription bias, and confounding by indication. Although baseline characteristics were comparable, unmeasured confounders such as disease trajectory, patient preference, or physician judgment cannot be entirely excluded. The unequal group sizes reflect real-world prescribing patterns but may introduce imbalance. Future prospective randomized controlled trials with balanced allocation are needed to confirm these findings. Second, the single-center design and moderate sample size may limit generalizability. Third, the

6-month follow-up captured symptomatic changes but was insufficient to assess long-term persistence or disease-modifying effects. Fourth, non-motor assessment was restricted to four self-report scales addressing depression, anxiety, fatigue, and daytime sleepiness. Core non-motor domains that are highly relevant to PD-including cognition, autonomic dysfunction (e.g., constipation, orthostatic hypotension), sleep architecture, and hyposmia-were not

evaluated due to incomplete documentation in the electronic medical records. Consequently, the non-motor findings should be interpreted strictly as reflecting improvements in the selected domains and should not be generalized to the full non-motor spectrum of PD. Whether rasagiline benefits cognitive, autonomic, or other non-motor domains remains an open question that requires prospective evaluation with comprehensive assessment tools such as the MDS-UPDRS Part I and domain-specific batteries. Fifth, although blood collection was standardized to morning fasting, the precise motor state (ON vs. OFF) at the moment of venipuncture could not be determined from the retrospective records. This is a critical confounder, as motor fluctuations and dopaminergic medication cycles dynamically influence immune cell trafficking, adhesion molecule expression, and systemic cytokine release. Circulating inflammatory markers (NLR, CRP, IL-6, and TNF- α) can vary with motor state, and circadian rhythms further modulate immune parameters. Consequently, the observed differences in inflammatory markers between the two groups may be partially attributable to non-uniform sampling with respect to motor state, rather than solely representing a true treatment-induced anti-inflammatory effect. This underscores the need for future prospective studies with strictly standardized blood collection protocols specifying both motor state and circadian time to minimize variability and improve biomarker reliability.

Conclusion

In conclusion, this retrospective study assessed the multifaceted effects of adding rasagiline to levodopa in PD patients with

motor fluctuations. Our findings indicate that adjunctive rasagiline was associated with favorable changes in motor function, several non-motor domains (depression, fatigue, and daytime sleepiness), quality of life, and systemic inflammatory markers, with a safety profile comparable to that of levodopa monotherapy. Notably, no significant between-group differences in adverse event frequencies were observed. These results suggest that rasagiline may be a well-tolerated adjunctive option with potential symptomatic benefits across multiple clinical dimensions. However, it is critical to emphasize that this was a retrospective, non-randomized study with a 6-month follow-up and a limited non-motor assessment battery. Consequently, our data do not support conclusions regarding disease-modifying, neuroprotective, or long-term effects. The observed associations should be viewed as preliminary and hypothesis-generating rather than definitive. Future prospective, randomized, double-blind, placebo-controlled trials with extended follow-up and comprehensive outcome assessments-including cognitive, autonomic, sleep, and olfactory domains-are essential to confirm these findings, establish causality, and determine whether the anti-inflammatory changes are mechanistically linked to clinical benefits.

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Disclosure of conflict of interest

None.

Address correspondence to: Xin Gao, School of Pharmacy, Heilongjiang University of Chinese Medicine, No. 24 Heping Road, Xiangfang District, Harbin 150040, Heilongjiang, China. E-mail: gao-hu900@163.com

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