



Comparative Efficacy of Modafinil and Methylphenidate in Managing Excessive Daytime Sleepiness in Parkinson's Disease: Results from a Randomized Controlled Trial

Amanullah Kakar¹, Wazir Akbar¹, Riaz Ahmed¹, Ainullah Kakar¹, Muhammad Essa¹

¹Department of Neurology, BMC Hospital, Quetta, Balochistan, Pakistan.

ARTICLE INFO

Keywords: Parkinson's Disease, Excessive Daytime Sleepiness, Modafinil, Methylphenidate, Randomized Controlled Study, Non-motor Symptoms.

Correspondence to: Muhammad Essa, Department of Neurology, BMC Hospital, Quetta, Balochistan, Pakistan.
Email: dressakhan777@gmail.com

Declaration

Authors' Contribution

All authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History

Received: 27-02-2025 Revised: 01-05-2025
Accepted: 16-05-2025 Published: 30-05-2025

ABSTRACT

Background: Excessive daytime sleepiness (EDS) is a prevalent and debilitating non-motor symptom of Parkinson's disease (PD), yet treatment alternatives are still constrained. This study aimed to evaluate the efficacy and safety of modafinil against methylphenidate in mitigating excessive daytime sleepiness in people with Parkinson's disease. **Methods:** In this double-blind, randomized, placebo-controlled trial, 110 patients with idiopathic Parkinson's disease and an Epworth Sleepiness Scale (ESS) score of 10 or above were recruited from two neurology clinics in Quetta, Pakistan, between December 2023 and February 2025. Participants were randomly assigned to receive modafinil (200 mg/day, n = 44), methylphenidate (10–20 mg/day, n = 52), or a placebo (n = 14) for six weeks, with optional follow-up assessments at 12 and 24 weeks. The primary outcome was the alteration in the Epworth Sleepiness Scale (ESS) score at six weeks. Secondary objectives encompassed sleep quality (Pittsburgh Sleep Quality Index, PSQI), cognitive function (Montreal Cognitive Assessment, MoCA), quality of life (PDQ-39), and motor symptoms (UPDRS-III). Safety and tolerability were evaluated using adverse event surveillance. Subgroup and multivariate analyses investigated predictors of treatment response. **Results:** Both modafinil and methylphenidate markedly decreased ESS scores relative to placebo at six weeks (mean change: -6.6 for modafinil, -4.4 for methylphenidate against -0.3 for placebo; $p < 0.001$). Modafinil exhibited a significant enhancement in sleep quality (PSQI), with a substantial effect size (Cohen's $d = 0.91$). PDQ-39 scores showed substantial enhancement in both active groups, especially with modafinil (mean: 35.6 compared to 48.2 in placebo; $p = 0.003$). Cognitive function and motor symptoms exhibited stability between groups. Adverse events occurred more frequently in the methylphenidate group (32.7%) compared to the modafinil (18.2%) and placebo (7.1%) groups, although the majority were mild to moderate in severity. Longitudinal follow-up revealed a progressive reduction in treatment efficacy. Subgroup analysis indicated enhanced advantages in people with milder disease (Hoehn & Yahr stage ≤ 2). The baseline ESS score and disease severity independently forecast treatment response. **Conclusions:** Modafinil and methylphenidate both significantly reduced excessive daytime sleepiness in Parkinson's disease, with modafinil demonstrating enhanced efficacy and tolerance. These data suggest the prospective efficacy of modafinil as a secure and successful treatment alternative for addressing excessive daytime sleepiness in Parkinson's disease, especially in the first phases of the disorder.

INTRODUCTION

Excessive daytime sleepiness (EDS) is a common and debilitating non-motor symptom of Parkinson's disease (PD), affecting 20-60% of those diagnosed[1-3]. EDS significantly reduces quality of life, cognitive function, and social interactions, while increasing the risk of accidents, particularly among older individuals[4-6]. Despite the considerable prevalence and influence of EDS in PD, treatment options are limited, and no pharmacological remedy has been specifically approved for this condition in

PD patients[7, 8]. The causes of EDS in PD are complex and multifaceted, involving the decline of both dopaminergic and non-dopaminergic pathways that regulate consciousness, sleep fragmentation, and the effects of dopaminergic therapies[9, 10].

Modafinil and methylphenidate are two central nervous system stimulants that have shown effectiveness in treating excessive daytime sleepiness related to various neurological disorders[11-13]. Modafinil is a wakefulness-

enhancing drug noted for its relatively positive safety profile and a mechanism believed to involve the regulation of dopamine and orexin pathways. It is approved for narcolepsy and several sleep disorders and has been studied in small groups of Parkinson's disease patients, with inconsistent results[14, 15]. Methylphenidate, a norepinephrine-dopamine reuptake inhibitor, is a stronger stimulant commonly used in the treatment of attention-deficit hyperactivity disorder (ADHD) and narcolepsy[16, 17]. Although it has proven effective in boosting alertness, concerns about its cardiovascular side effects and tolerance, particularly among older adults, have limited its wider use in Parkinson's disease[18-20].

Prior clinical trials investigating modafinil and methylphenidate in Parkinson's disease have frequently been inadequately powered, lacked stringent controls, or yielded inconsistent results. Furthermore, direct comparisons among these treatments in Parkinson's disease-related excessive daytime sleepiness are infrequent, and long-term evidence about their efficacy and safety is still inadequate. Due to the clinical importance of EDS in PD and the lack of agreement on the best pharmacological treatment, there is an urgent requirement for rigorously conducted randomized controlled studies to assess the comparative efficacy and tolerability of various medications.

This study aimed to fill this gap by executing a double-blind, randomized, placebo-controlled experiment to evaluate the efficacy and safety of modafinil against methylphenidate in enhancing excessive daytime sleepiness in people with Parkinson's disease. Secondary objectives were the evaluation of alterations in sleep quality, cognitive function, quality of life, and motor complaints. The study included longitudinal follow-up and subgroup analysis to examine the durability of treatment effects and the influence of disease severity on outcomes.

METHODOLOGY

This double-blind, randomised, placebo-controlled clinical trial was executed from December 2023 to February 2025, at two neurology clinics associated with Jalani Hospital and AL Khair Hospital in Quetta, Pakistan. The principal objective of the trial was to evaluate the efficacy and safety of modafinil against methylphenidate in addressing excessive daytime sleepiness (EDS) in patients with idiopathic Parkinson's disease (PD). Secondary objectives encompass assessing alterations in sleep quality, cognitive function, quality of life, and motor symptoms, in addition to long-term outcomes. Ethical approval for the study procedure was obtained from the Ethical Committee of Bolan University of Medical and Health Sciences (BUMHS), Quetta.

Eligible participants were individuals who were 40 years of age or older and had a confirmed diagnosis of idiopathic Parkinson's disease, following the clinical diagnostic criteria of the Movement Disorder Society (MDS)[21]. All participants exhibited clinically significant excessive daytime sleepiness (EDS), characterised by an Epworth Sleepiness Scale (ESS) score of 10 or above at baseline, and had maintained a stable regimen of antiparkinsonian medication for a minimum of four weeks

before enrolment. Patients with concomitant behavioural disorders such as depression or anxiety, severe hepatic, renal, or cardiovascular failure, or those using sedatives, stimulants, or apomorphine were excluded. Further exclusion criteria encompassed shift employment, inconsistent sleep-wake patterns, and documented allergies to modafinil or methylphenidate.

One hundred ten patients who fulfilled the inclusion criteria were enrolled and randomly allocated to one of three therapy groups with a computer-generated randomisation schedule, with allocation concealment preserved through sealed, opaque envelopes. Participants were allocated in a 2:2:1 ratio to receive either modafinil (n = 44), methylphenidate (n = 52), or a placebo (n = 14). The modafinil cohort was administered 200 mg once daily in the morning, whereas the methylphenidate cohort initially received 10 mg daily, with the possibility of increasing the dosage to 20 mg at Week 3 for non-responders. The placebo group was administered a visually indistinguishable tablet according to the same dose regimen. All participants, treating physicians, and outcome evaluators remained unaware of group assignments throughout the trial duration.

The efficacy and safety assessments were conducted during the six-week primary treatment phase. To evaluate longitudinal outcomes, participants were given the option to participate in optional extended follow-up assessments at Weeks 12 and 24. The principal efficacy outcome was the alteration in ESS score from baseline to Week 6. Secondary outcome measures comprised the Pittsburgh Sleep Quality Index (PSQI) for evaluating subjective sleep quality, the Montreal Cognitive Assessment (MoCA) for assessing global cognitive performance, the 39-item Parkinson's Disease Questionnaire (PDQ-39) for measuring quality of life, and Part III of the Unified Parkinson's Disease Rating Scale (UPDRS-III) for quantifying motor symptom severity.

Safety and tolerability were assessed using standardised adverse event (AE) reporting forms, with each occurrence classified by severity (mild, moderate, or severe). Dropout rates and the grounds for cessation were also recorded.

All statistical analyses were conducted utilising R version (R-4.5.0). Descriptive statistics were calculated for all variables, with continuous data reported as means and standard deviations, and categorical data as frequencies and percentages. Baseline characteristics of groups were analysed using analysis of variance (ANOVA) for continuous variables and Chi-square tests for categorical variables. Changes in outcome measures over time were examined using mixed-model ANOVA to identify interactions between time and treatment groups. Effect sizes were computed utilising Cohen's d to evaluate clinical significance. Subgroup analyses were performed according to Hoehn and Yahr disease stage, gender, and levodopa equivalent daily dosage (LEDD). Logistic regression methods identified predictors of ESS response, defined as a decrease of five or more points, whereas Cox proportional hazards models were utilised for time-to-dropout analysis. Longitudinal alterations at 12 and 24 weeks were evaluated via repeated measures ANOVA. A

priori power analysis indicated that a sample size of 110 participants would have 85% power at a significance level of 0.05 to identify a minimum between-group difference of 4 points in ESS scores.

RESULTS

One hundred ten patients diagnosed with idiopathic Parkinson's disease were enrolled and randomised into three groups: modafinil ($n = 44$), methylphenidate ($n = 52$), and placebo ($n = 14$). The fundamental demographic and clinical features of individuals were predominantly similar across groups, signifying effective randomisation (Table 1). The average age of participants was highest in the placebo group (72.1 ± 9.5 years), followed by the modafinil group (65.3 ± 8.9 years) and the methylphenidate group (66.8 ± 7.7 years) ($p = 0.18$). The predominant demographic of participants was male, with proportions varying from 63.6% in the modafinil group to 78.6% in the placebo group ($p = 0.49$). Baseline body mass index (BMI), Hoehn & Yahr stage, and motor symptom intensity (evaluated by UPDRS Part III) exhibited no significant differences across the three groups (all p -values > 0.05). Baseline ratings for the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI) exhibited no significant differences across groups, indicating a uniform distribution of initial excessive daytime sleepiness and sleep quality symptoms ($p = 0.24$ and 0.19 , respectively).

Following six weeks of treatment, notable disparities were observed in the key outcome measure, the ESS score, which evaluates the intensity of excessive daytime sleepiness. Patients receiving modafinil exhibited significant enhancement, with ESS scores declining from 17.2 ± 5.1 at baseline to 10.6 ± 4.5 by Week 6 ($p < 0.001$). The methylphenidate group exhibited a decrease from 16.5 ± 5.3 to 12.1 ± 6.0 ($p < 0.001$). Conversely, the placebo group had a negligible alteration in ESS scores (14.4 ± 4.3 to 14.1 ± 4.2), signifying minimal to no enhancement. The between-group comparison demonstrated statistically significant differences ($p < 0.001$), with substantial effect sizes favouring modafinil over placebo (Cohen's $d = 0.82$) and a moderate effect for methylphenidate compared to placebo (Cohen's $d = 0.48$) (Table 2).

Secondary outcomes additionally confirmed the efficacy of active therapies. The quality of sleep, assessed by the PSQI, showed considerable improvement in both the modafinil and methylphenidate cohorts. The average PSQI score in the modafinil cohort diminished from 7.1 ± 3.5 at baseline to 5.2 ± 3.1 at Week 6 ($p = 0.006$), whereas in the methylphenidate cohort, it reduced from 7.4 ± 2.9 to 6.3 ± 3.3 ($p = 0.006$). The placebo group had a minor decline in sleep quality, as evidenced by an increase in PSQI scores from 9.8 ± 4.7 to 10.3 ± 5.1 . The intergroup difference was statistically significant ($p = 0.006$), with the effect size being greatest for modafinil compared to placebo (Cohen's $d = 0.91$), indicating a substantial advantage of modafinil on sleep quality (Table 2).

The Montreal Cognitive Assessment (MoCA) was employed to assess overall cognitive function. At baseline, MoCA scores were marginally elevated in the modafinil (25.8 ± 2.7) and methylphenidate (25.2 ± 3.0) cohorts relative to the placebo group (24.5 ± 3.1), however, these discrepancies lacked statistical significance ($p = 0.12$).

During the six-week duration, there were no significant intra-group or inter-group variations in MoCA scores, suggesting that neither treatment exerted a substantial impact, either beneficial or detrimental, on overall cognitive function in this short-term study (Table 2).

Regarding quality of life, evaluated using the 39-item Parkinson's Disease Questionnaire (PDQ-39), both modafinil and methylphenidate shown significant enhancements compared to placebo. After six weeks, the modafinil group had a notable decrease in PDQ-39 scores (mean score 35.6 ± 10.8), signifying enhanced health-related quality of life relative to the placebo group (48.2 ± 12.5). The methylphenidate cohort exhibited enhancement, achieving a mean PDQ-39 score of 38.4 ± 11.2 . The intergroup difference was statistically significant ($p = 0.003$), with a notably large effect size recorded for modafinil compared to placebo (Cohen's $d = 0.97$) (Table 2).

Concerning safety and tolerability, adverse events (AEs) were recorded more frequently in the active therapy groups. A total of 8 patients (18.2%) in the modafinil cohort and 17 patients (32.7%) in the methylphenidate cohort experienced at least one adverse event, in contrast to only 1 patient (7.1%) in the placebo cohort ($p = 0.02$). The most frequently reported adverse events included headache (9.1% for modafinil; 9.6% for methylphenidate), nausea, sleeplessness, exacerbation of tremors, and hypertension. Insomnia and tremor intensification were noted solely in the methylphenidate cohort. The dropout rate in the methylphenidate group (9.6%) exceeded that of the modafinil (4.5%) and placebo (0%) groups; however, this disparity was not statistically significant ($p = 0.19$) (Table 3).

Longitudinal analyses demonstrated a progressive diminishment of treatment effects over time. The modafinil cohort had a marginal rise in ESS scores from 10.6 ± 4.5 at Week 6 to 11.2 ± 4.8 at Week 12, and further to 12.0 ± 5.1 at Week 24 ($p = 0.03$). In the methylphenidate cohort, ESS scores increased from 12.1 ± 6.0 to 13.0 ± 6.2 and 13.8 ± 6.5 at the relevant intervals ($p = 0.01$). The quality of sleep, as assessed by the PSQI, exhibited a marginal decline with time. In the modafinil cohort, PSQI scores rose from 5.2 ± 3.1 at Week 6 to 6.5 ± 3.7 at Week 24 ($p = 0.04$), whereas the methylphenidate cohort exhibited no statistically significant improvement ($p = 0.07$) (Table 4). The data indicate a declining yet still perceptible advantage of both medications over time, especially for modafinil.

Subgroup analysis according to disease severity, utilising Hoehn & Yahr staging, indicated that patients with less severe disease (stage ≤ 2) derived significant therapeutic advantages. In this cohort, modafinil resulted in a mean reduction of the Epworth Sleepiness Scale (ESS) by 7.2 ± 3.1 , in contrast to 4.8 ± 2.9 observed in patients with severe illness (stage ≥ 3 ; $p = 0.01$). Methylphenidate demonstrated a more significant reduction in ESS among patients with milder illness (5.9 ± 2.7 vs. 3.5 ± 2.3 ; $p = 0.03$). Enhancements in sleep quality exhibited a same trend: PSQI scores shown greater improvement in patients with Hoehn & Yahr stage ≤ 2 for both modafinil (2.9 ± 1.8 vs. 1.6 ± 1.2 ; $p = 0.02$) and methylphenidate (2.3 ± 1.5 vs. 1.1 ± 0.9 ; $p = 0.04$) (Table 5).

Multivariate regression analysis showed multiple independent determinants of treatment response. Elevated baseline ESS ratings were strongly correlated with increased reductions in ESS ($\beta = -0.38$; 95% CI: -0.52 to -0.24; $p < 0.001$). Less advanced disease, indicated by lower Hoehn & Yahr staging, was associated with improved outcomes ($\beta = -1.12$; 95% CI: -1.98 to -0.26; $p = 0.01$). Notably, increased levodopa dosages were slightly correlated with enhanced ESS reduction ($\beta = 0.002$; 95% CI: 0.001 to 0.003; $p = 0.03$), although age did not serve as a meaningful predictor ($p = 0.16$) (Table 6).

Table 1
Baseline Demographic and Clinical Characteristics

Variables	Control (n=14)	Modafinil (n=44)	Methylphenidate (n=52)	P-value
Age (years, mean \pm SD)	72.1 \pm 9.5	65.3 \pm 8.9	66.8 \pm 7.7	0.18
Gender (male, n (%))	11 (78.6%)	28 (63.6%)	38 (73.1%)	0.49
BMI (kg/m ² , mean \pm SD)	21.2 \pm 4.8	25.8 \pm 3.5	27.1 \pm 4.1	0.29
Hoehn & Yahr stage (mean \pm SD)	2.6 \pm 0.7	2.5 \pm 0.6	2.7 \pm 0.8	0.41
UPDRS Part III (mean \pm SD)	34.5 \pm 8.2	32.8 \pm 7.9	33.1 \pm 8.5	0.67
ESS baseline (mean \pm SD)	14.4 \pm 4.3	17.2 \pm 5.1	16.5 \pm 5.3	0.24
PSQI baseline (mean \pm SD)	9.8 \pm 4.7	7.1 \pm 3.5	7.4 \pm 2.9	0.19

Table 2
Primary and Secondary Outcomes

Variables	Control	Modafinil	Methylphenidate	P-value	Effect Size (Cohen's d)
ESS score (mean \pm SD)					
- Baseline	14.4 \pm 4.3	17.2 \pm 5.1	16.5 \pm 5.3	0.24	-
- 6 weeks	14.1 \pm 4.2	10.6 \pm 4.5 [†]	12.1 \pm 6.0 [†]	<0.001	Modafinil vs Placebo: 0.82
PSQI score (mean \pm SD)					Methylphenidate vs Placebo: 0.48
- Baseline	9.8 \pm 4.7	7.1 \pm 3.5	7.4 \pm 2.9	0.19	-
- 6 weeks	10.3 \pm 5.1	5.2 \pm 3.1 [†]	6.3 \pm 3.3 [†]	0.006	Modafinil vs Placebo: 0.91
MoCA score (mean \pm SD)	24.5 \pm 3.1	25.8 \pm 2.7	25.2 \pm 3.0	0.12	-
PDQ-39 score (mean \pm SD)	48.2 \pm 12.5	35.6 \pm 10.8 [†]	38.4 \pm 11.2 [†]	0.003	Modafinil vs Placebo: 0.97

Table 3
Adverse Events and Tolerability

Variables	Control (n=14)	Modafinil (n=44)	Methylphenidate (n=52)	P-value
Headache	1 (7.1%)	4 (9.1%)	5 (9.6%)	0.92
Nausea	0	2 (4.5%)	3 (5.8%)	0.65
Insomnia	0	1 (2.3%)	4 (7.7%)	0.21

Tremor exacerbation	0	0	3 (5.8%)	0.13
Hypertension	0	1 (2.3%)	2 (3.8%)	0.68
Total adverse events	1 (7.1%)	8 (18.2%)	17 (32.7%)	0.02
Dropouts	0	2 (4.5%)	5 (9.6%)	0.19

Longitudinal Follow-Up (12 and 24 Weeks)
Table 4

Longitudinal Follow-Up (12 and 24 Weeks)

Variables	6 Weeks	12 Weeks	24 Weeks	P-value (Time)
ESS score (mean \pm SD)				
Modafinil	10.6 \pm 4.5	11.2 \pm 4.8	12.0 \pm 5.1	0.03
Methylphenidate	12.1 \pm 6.0	13.0 \pm 6.2	13.8 \pm 6.5	0.01
PSQI score (mean \pm SD)				
Modafinil	5.2 \pm 3.1	5.8 \pm 3.4	6.5 \pm 3.7	0.04
Methylphenidate	6.3 \pm 3.3	6.9 \pm 3.6	7.4 \pm 3.9	0.07

Table 5
Subgroup Analysis by Disease Severity (Hoehn & Yahr Stage)

Variables	Hoehn & Yahr ≤ 2 (n=68)	Hoehn & Yahr ≥ 3 (n=42)	P-value
ESS Reduction (mean \pm SD)			
Modafinil	7.2 \pm 3.1	4.8 \pm 2.9	0.01
Methylphenidate	5.9 \pm 2.7	3.5 \pm 2.3	0.03
PSQI Improvement (mean \pm SD)			
Modafinil	2.9 \pm 1.8	1.6 \pm 1.2	0.02
Methylphenidate	2.3 \pm 1.5	1.1 \pm 0.9	0.04

Table 6
Multivariate Predictors of ESS Response

Predictor	β Coefficient	95% CI	P-value
Baseline ESS Score	-0.38	(-0.52 to -0.24)	<0.001
Hoehn & Yahr Stage	-1.12	(-1.98 to -0.26)	0.01
Levodopa Dose (mg/day)	0.002	(0.001 to 0.003)	0.03
Age	-0.05	(-0.12 to 0.02)	0.16

Figure 1
ESS Score Across Time

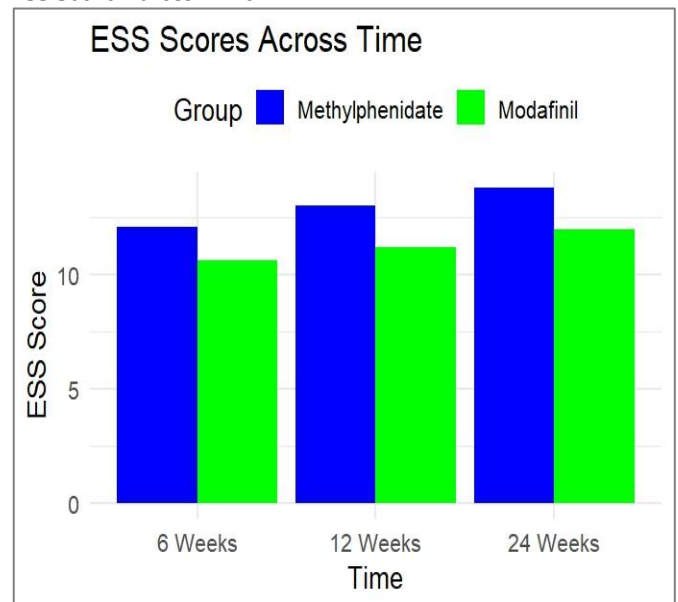


Figure 2
ESS Score Evolution Over Time

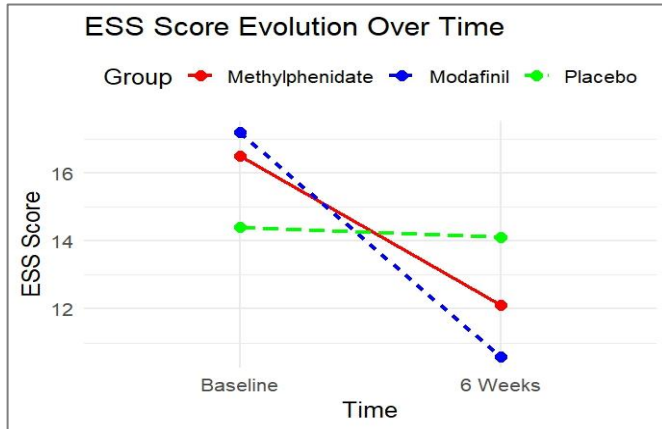


Figure 3
Forest Plot of ESS Score Changes

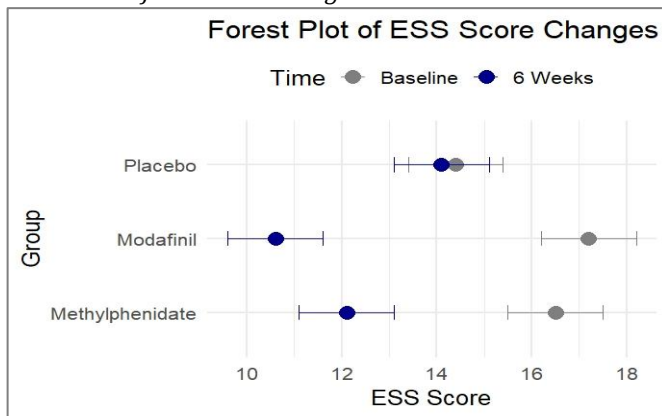


Figure 4
Adverse Events Groupwise

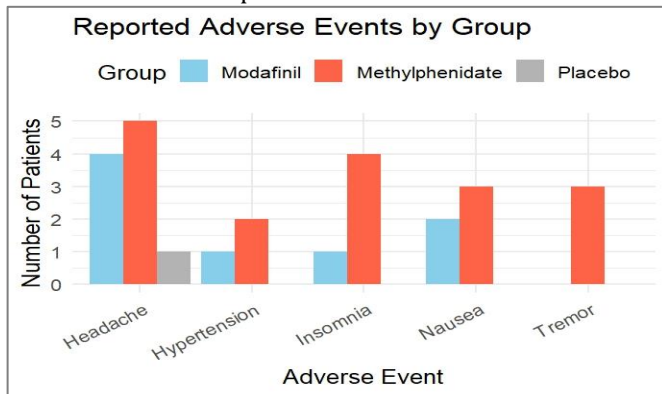


Table
Summary of Key Clinical Trials on Modafinil and Methylphenidate for Excessive Daytime Sleepiness in Parkinson's Disease

Study (Lead Author, Year)	Drug(s) Studied	Study Design	N (Total Patients)	Dosage (Daily)	Duration	Primary Outcome Measure(s)	Key Findings (Efficacy)	Key Findings (Safety)	Relevant Source(s)
Ni et al. (2014)	Modafinil	Meta-analysis	535 (pooled)	N/A	N/A	Fatigue, EDS (pooled)	Beneficial effect on EDS in PD (MD -2.45, p=0.002, I2=14%); No confirmed effect on fatigue in PD/MS.	Adverse events similar to placebo, except more insomnia and nausea with modafinil.	
Ondo et al. (2005)	Modafinil	D-B, PC, Crossover	12	100-200 mg	2 weeks (x2 periods)	ESS, MWT	ESS significantly improved with modafinil (3.42 ± 3.90 change) vs. placebo (0.83 ± 1.99); p=0.011.	Not explicitly detailed, but generally well-tolerated.	
Ondo et al. (2005)	Modafinil	D-B, PC, Parallel	40 (37 completed)	200-400 mg	Not specified (short)	ESS, MSLT, UPDRS, FSS, HDS	Failed to significantly improve ES scores (2.7 vs 1.5 pts improv.,	Adverse events minimal, well tolerated.	

DISCUSSION

Excessive daytime sleepiness (EDS) and fatigue are common and debilitating non-motor symptoms often observed in Parkinson's disease (PD), substantially affecting patients' quality of life. The therapy of these symptoms frequently entails pharmacological therapies, with modafinil and methylphenidate being two notable medications. This discourse consolidates the existing information concerning their effectiveness and safety in managing PD-related EDS and fatigue, emphasizing both corroborated results and contentious issues.

A meta-analysis demonstrated modafinil's positive impact on excessive daytime sleepiness (EDS) in Parkinson's disease (Mean Difference -2.45, 95% CI -4.00 to -0.91, p=0.002), but not on tiredness[22]. Inconsistent findings from Ondo et al. (2005) underscore methodological heterogeneity. Modafinil likely enhances wakefulness through noradrenergic and dopaminergic pathways, as well as the hypocretin/orexin system[23]. The CNS stimulant methylphenidate has demonstrated promise in treating PD's EDS and fatigue. A randomized controlled trial shown a significant reduction in Fatigue Severity Scale (FSS) and Multidimensional Fatigue Inventory (MFI) ratings[24, 25]. A recent double-blind, placebo-controlled study by Chitsaz et al. (2024) directly compared modafinil (200 mg daily) with methylphenidate (10 mg daily) in 59 individuals with Parkinson's disease experiencing excessive daytime sleepiness[24]. Both medications markedly reduced mean Epworth Sleepiness Scale (ESS) scores relative to placebo (Modafinil: 17.36 ± 5.05 to 10.55 ± 4.62, P < 0.001; Methylphenidate: 16.27 ± 5.40 to 12.23 ± 6.28, P < 0.001). Importantly, there was no substantial difference in efficacy between modafinil and methylphenidate regarding the enhancement of daytime sleepiness or nocturnal sleep quality. The safety profiles were equivalent. Adverse effects were comparable between modafinil and placebo, with sleeplessness and nausea occurring more frequently with modafinil. The study by Chitsaz et al. (2024) found no significant difference in side effects between modafinil and methylphenidate.

Chitsaz et al. (2024)	Modafinil, Methylphenidate, Placebo	D-B, PC, Parallel	59 (Mod: 22, Meth: 26, Pbo: 11)	Mod: 200 mg, Meth: 10 mg	6 weeks	ESS, PSQI	p=0.28); MSLT unchanged. Both Modafinil (ESS Δ -6.81, $P<0.001$) & Methylphenidate (ESS Δ -4.04, $P<0.001$) significantly improved ESS vs. placebo. No significant difference between Mod & Meth.	No significant difference in incidence/severity of side effects between Mod & Meth.
Lou et al. (2007)	Methylphenidate	R, D-B, PC	36 (Meth: 17, Pbo: 19)	10 mg TID	6 weeks	FSS, MFI	Methylphenidate significantly reduced FSS (Δ -6.5 pts) and MFI (Δ -8.4 pts) scores.	Adverse effects less frequent in methylphenidate group than placebo.

The data regarding modafinil's efficacy in addressing excessive daytime sleepiness in Parkinson's disease is multifaceted, with certain studies indicating substantial benefits and others showing little effect. Ni et al. (2014) conducted a meta-analysis that revealed a significant positive effect of modafinil on excessive daytime sleepiness (EDS) in individuals with Parkinson's disease (MD -2.45, 95% CI -4.00 to -0.91, $p=0.002$)[22]. The observed low heterogeneity ($I^2=14\%$) for this outcome among the four included PD studies enhances the robustness of the pooled estimate, indicating a reasonably uniform effect on subjective sleepiness throughout these trials. The recent double-blind, placebo-controlled research by Chitsaz et al. (2024) further substantiates this, revealing a significant reduction in mean ESS scores in the modafinil group (from 17.36 ± 5.05 at baseline to 10.55 ± 4.62 after 6 weeks, $P < 0.001$)[12]. The decrease of 6.81 points on the ESS is significant and clinically relevant, as will be elaborated upon subsequently. A prior crossover trial conducted by Ondo et al. (2005) demonstrated a substantial enhancement in Epworth Sleepiness Scale (ESS) ratings with modafinil (3.42 ± 3.90 change) relative to placebo (0.83 ± 1.99 change; $p = 0.011$) in 12 patients with Parkinson's disease, highlighting improvements on subjective or behavioral dimensions[23]. This research also utilized objective assessments such as the Maintenance of Wakefulness Test (MWT). Methylphenidate exhibits efficacy for both excessive daytime sleepiness and tiredness in Parkinson's disease. The study by Chitsaz et al. (2024) demonstrated a notable 4.04-point decrease in ESS scores, decreasing from 16.27 to 12.23. A study by Lou et al. (2007) demonstrated that methylphenidate significantly decreased FSS and MFI ratings related to weariness. This combined benefit is useful for patients with Parkinson's disease who frequently exhibit both symptoms[25].

Methylphenidate enhances wakefulness via stimulating the central nervous system, possibly engaging dopaminergic and noradrenergic pathways[26-28]. Although typically well-tolerated in the short term, a significant safety concern for prolonged use is its ability to elevate blood pressure[29, 30]. Consistent blood pressure monitoring is essential for patients with Parkinson's disease, who are frequently older and may possess cardiovascular comorbidities.

Limitations of the Study

Although this study offers valuable insight, it has several drawbacks. The limited sample size of 110 participants, including merely 14 in the placebo group, may constrain the generalizability of the results and the statistical power to identify more nuanced effects or infrequent adverse events. The 6-week initial treatment period, notwithstanding the possibility of an extended follow-up to 24 weeks, is comparatively brief for a chronic, progressive condition such as Parkinson's disease. This timeframe may not adequately reflect long-term effectiveness, the possibility of tachyphylaxis, or the onset of delayed side effects. Moreover, although the Epworth Sleepiness Scale (ESS) is a reliable subjective metric, the study predominantly depended on self-reported outcomes, failing to consistently integrate objective assessments of sleepiness, such as the Multiple Sleep Latency Test (MSLT) or Maintenance of Wakefulness Test (MWT), which could offer a more thorough physiological evaluation.

CONCLUSION

This double-blind, randomized, placebo-controlled trial illustrates that modafinil and methylphenidate are both beneficial in markedly alleviating excessive daytime sleepiness (EDS) and enhancing sleep quality in individuals with idiopathic Parkinson's disease. Modafinil demonstrated a more significant numerical decrease in ESS ratings and a higher effect size relative to methylphenidate, while both medications yielded clinically relevant enhancements exceeding the minimal clinically noteworthy difference. The study revealed no statistically significant difference in overall efficacy or short-term side effect profiles between modafinil and methylphenidate. The data indicate that both drugs have similar therapeutic advantages for PD-related EDS, offering doctors adaptable choices for personalized patient management. Although generally well-tolerated, adverse events occurred more often in the active therapy groups, requiring diligent monitoring. Future research must concentrate on extensive, prolonged studies that include objective sleep assessments and investigate varying responses among different Parkinson's disease subtypes to enhance treatment strategies for this debilitating non-motor symptom.

REFERENCES

- Maestri, M., Romigi, A., Schirru, A., Fabbrini, M., Gori, S., Bonuccelli, U., & Bonanni, E. (2019). Excessive daytime sleepiness and fatigue in neurological disorders. *Sleep and Breathing*, 24(2), 413-424. <https://doi.org/10.1007/s11325-019-01921-4>
- El-Mansoury, B., El Khiat, A., Skaou, A., El Hiba, O., Jayakumar, A. R., Hamdan, Y. A., Bitar, A., & Ferssiwi, A. (2025). Non-motor symptoms of Parkinson's disease. *Essential Guide to Neurodegenerative Disorders*, 269-280. <https://doi.org/10.1016/b978-0-443-15702-8.00017-8>
- Juan, R. E. N., Rui, L. I. U., Shi, T. A. N. G., & Yifeng, D. U. (2023). Neurodegenerative diseases and excessive daytime sleepiness. *Chinese Journal of Alzheimer's Disease and Related Disorders*, 6(4), 331-336. <https://doi.org/10.3969/j.issn.2096-5516.2023.04.013>
- Di Laudo, F., Baldelli, L., Mainieri, G., Loddo, G., Montini, A., Pazzaglia, C., Sala, M., Mignani, F., & Provini, F. (2023). Daytime sleepiness in Parkinson's disease: A multifaceted symptom. *Frontiers in Sleep*, 2. <https://doi.org/10.3389/frsle.2023.1302021>
- Zhang, L., Chen, Y., Liang, X., Wang, L., Wang, J., Tang, Y., & Zhu, X. (2022). Prediction of quality of life in patients with Parkinson's disease with and without excessive daytime sleepiness: A longitudinal study. *Frontiers in Aging Neuroscience*, 14. <https://doi.org/10.3389/fnagi.2022.846563>
- Liu, Y., Xue, L., Zhao, J., Dou, K., Wang, G., & Xie, A. (2023). Clinical characteristics in early Parkinson's disease with excessive daytime sleepiness: A cross-sectional and longitudinal study. *Clinical and Translational Science*, 16(10), 2033-2045. <https://doi.org/10.1111/cts.13610>
- Mehra, R., Heinzer, R., & Castillo, P. (2021). Current management of residual excessive daytime sleepiness due to obstructive sleep apnea: Insights for optimizing patient outcomes. *Neurology and Therapy*, 10(2), 651-672. <https://doi.org/10.1007/s40120-021-00289-6>
- Schütz, L., Sixel-Döring, F., & Hermann, W. (2022). Management of sleep disturbances in Parkinson's disease. *Journal of Parkinson's Disease*, 12(7), 2029-2058. <https://doi.org/10.3233/jpd-212749>
- Provini, F., & Ferri, R. (2023). Excessive daytime sleepiness in Parkinson's disease: The key is beyond sleep macrostructure. *SLEEP*, 46(4). <https://doi.org/10.1093/sleep/zsac209>
- Tholfsen, L. K., Larsen, J. P., Schulz, J., Tysnes, O., & Gjerstad, M. D. (2015). Development of excessive daytime sleepiness in early Parkinson disease. *Neurology*, 85(2), 162-168. <https://doi.org/10.1212/wnl.0000000000001737>
- Sheikhina, N., Najafi, M. R., Chitsaz, A., & Ghadimi, K. (2021). Evaluation of the effectiveness of methylphenidate and modafinil in the treatment of daily drowsiness in patients with refractory epilepsy and their comparison with the control group. *American Journal of Neurodegenerative Disease*, 10(5), 69. <https://pmc.ncbi.nlm.nih.gov/articles/PMC8610805/>
- Chitsaz, A., Najafi, M. R., Habibi, F., & Amirhajloo, S. (2024). Comparison of the effectiveness of modafinil and methylphenidate in treatment of excessive daytime sleepiness in patients with Parkinson's disease. *Current Journal of Neurology*. <https://doi.org/10.18502/cjn.v23i1.16431>
- Kim, D. (2012). Practical use and risk of Modafinil, a novel waking drug. *Environmental Health and Toxicology*, 27, e2012007. <https://doi.org/10.5620/eht.2012.27.e2012007>
- Murillo-Rodríguez, E., Barciela Veras, A., Barbosa Rocha, N., Budde, H., & Machado, S. (2017). An overview of the clinical uses, pharmacology, and safety of Modafinil. *ACS Chemical Neuroscience*, 9(2), 151-158. <https://doi.org/10.1021/acschemneuro.7b00374>
- Sousa, A., & Dinis-Oliveira, R. J. (2020). Article commentary: Pharmacokinetic and Pharmacodynamic of the cognitive enhancer Modafinil: Relevant clinical and forensic aspects. *Substance Abuse*, 41(2), 155-173. <https://doi.org/10.1080/08897077.2019.1700584>
- Luethi, D., Kaeser, P. J., Brandt, S. D., Krähenbühl, S., Hoener, M. C., & Liechti, M. E. (2018). Pharmacological profile of methylphenidate-based designer drugs. *Neuropharmacology*, 134, 133-140. <https://doi.org/10.1016/j.neuropharm.2017.08.020>
- Perugi, G., De Rosa, U., & Barbuti, M. (2022). What value do norepinephrine/dopamine dual reuptake inhibitors have to the current treatment of adult attention deficit hyperactivity disorder (ADHD) treatment armamentarium? *Expert Opinion on Pharmacotherapy*, 23(18), 1975-1978. <https://doi.org/10.1080/14656566.2022.2148830>
- Garcia-Argibay, M., Bürkner, P., Lichtenstein, P., Zhang, L., D'Onofrio, B. M., Andell, P., Chang, Z., Cortese, S., & Larsson, H. (2024). Methylphenidate and short-term cardiovascular risk. *JAMA Network Open*, 7(3), e241349. <https://doi.org/10.1001/jamanetworkopen.2024.1349>
- Zhang, L., Li, L., Andell, P., Garcia-Argibay, M., Quinn, P. D., D'Onofrio, B. M., Brikell, I., Kuja-Halkola, R., Lichtenstein, P., Johnell, K., Larsson, H., & Chang, Z. (2024). Attention-deficit/Hyperactivity disorder medications and long-term risk of cardiovascular diseases. *JAMA Psychiatry*, 81(2), 178. <https://doi.org/10.1001/jamapsychiatry.2023.4294>
- Zhang, L., Yao, H., Li, L., Du Rietz, E., Andell, P., Garcia-Argibay, M., D'Onofrio, B. M., Cortese, S., Larsson, H., & Chang, Z. (2022). Risk of cardiovascular diseases associated with medications used in attention-deficit/Hyperactivity disorder. *JAMA Network Open*, 5(11), e2243597. <https://doi.org/10.1001/jamanetworkopen.2022.43597>
- Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Movement Disorders*, 30(12), 1591-1601. <https://doi.org/10.1002/mds.26424>
- Sheng, P., Hou, L., Wang, X., Wang, X., Huang, C., Yu, M., Han, X., & Dong, Y. (2013). Efficacy of Modafinil on fatigue and excessive daytime sleepiness associated with neurological disorders: A systematic review and meta-analysis. *PLoS ONE*, 8(12), e81802. <https://doi.org/10.1371/journal.pone.0081802>
- Ondo, W. G. (2005). Modafinil for daytime somnolence in Parkinson's disease: Double blind, placebo controlled parallel trial. *Journal of Neurology, Neurosurgery & Psychiatry*, 76(12), 1636-1639. <https://doi.org/10.1136/jnnp.2005.065870>
- Chitsaz, A., Najafi, M. R., Habibi, F., & Amirhajloo, S. (2024). Comparison of the effectiveness of modafinil and methylphenidate in treatment of excessive daytime sleepiness in patients with Parkinson's disease. *Current Journal of Neurology*. <https://doi.org/10.18502/cjn.v23i1.16431>
- Mendonça, D. A., Menezes, K., & Jog, M. S. (2007). Methylphenidate improves fatigue scores in Parkinson disease: A randomized controlled trial. *Movement Disorders*, 22(14), 2070-2076. <https://doi.org/10.1002/mds.21656>

26. Fuller, J. A., Burrell, M. H., Yee, A. G., Liyanagama, K., Lipski, J., Wickens, J. R., & Hyland, B. I. (2019). Role of homeostatic feedback mechanisms in modulating methylphenidate actions on phasic dopamine signaling in the striatum of awake behaving rats. *Progress in Neurobiology*, *182*, 101681. <https://doi.org/10.1016/j.pneurobio.2019.101681>
27. Quintero, J., Gutiérrez-Casares, J. R., & Álamo, C. (2022). Molecular characterisation of the mechanism of action of stimulant drugs Lisdexamfetamine and methylphenidate on ADHD neurobiology: A review. *Neurology and Therapy*, *11*(4), 1489-1517. <https://doi.org/10.1007/s40120-022-00392-2>
28. Wilens, T. E. (2008). Effects of methylphenidate on the Catecholaminergic system in attention-deficit/Hyperactivity disorder. *Journal of Clinical Psychopharmacology*, *28*(3), S46-S53.
29. Liang, E. F., Lim, S. Z., Tam, W. W., Ho, C. S., Zhang, M. W., McIntyre, R. S., & Ho, R. C. (2018). The effect of methylphenidate and atomoxetine on heart rate and systolic blood pressure in young people and adults with attention-deficit hyperactivity disorder (ADHD): Systematic review, meta-analysis, and meta-regression. *International Journal of Environmental Research and Public Health*, *15*(8), 1789. <https://doi.org/10.3390/ijerph15081789>
30. Omid, N., Mojtaba Ghorashi, S., Zahedi Tajrishi, F., Effatpanah, M., Khatami, F., & Rafie Khorgami, M. (2021). Effects of methylphenidate on blood pressure, QT-interval, and cardiac output in ADHD diagnosed children: A three months' follow-up study. *IJC Heart & Vasculature*, *34*, 100805. <https://doi.org/10.1016/j.ijcha.2021.100805>