BMC Complementary Medicine and Therapies

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Efficacy and safety of Wuling capsule for the treatment of mild depression in patients with early Parkinson's disease in China: a randomized clinical trial

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Abstract

Background Depression is a prevalent non-motor symptom of Parkinson's disease (PD) that significantly impacts patients' quality of life. The Wuling capsule, a traditional Chinese medicine, is often utilized for treating depression, and this herbal medicine has been used to treat those PD patients with depression. This study aims to assess the efficacy and safety of Wuling capsule in treating mild depression in patients with early PD.

Methods This multicenter, double-blind, placebo-controlled randomized clinical trial included 160 patients with early PD who presented with a Hamilton Rating Scale for Depression (HAMD) score between 8 and 17 at the time of admission. The trial was conducted across five hospitals in China from December 2021 to March 2024. Eligible patients were randomly assigned to receive either Wuling capsule (0.99 g orally three times daily) or a placebo (0.99 g orally three times daily) for a duration of 12 weeks. Additional treatment according to established clinical guidelines.The primary outcome measure was the change in HAMD score. All statistical analyses were conducted on an intention-to-treat population.

Results After 12 weeks of treatment, among the 160 patients with early PD and depression, 80 were assigned to the Wuling capsule group and 80 to the placebo group, with the median age of 70.5 (IQR,67.00–75.00) years and 77 (48.13%) were male. Patients in the Wuling capsule group demonstrated significantly greater reductions in depression severity compared to the placebo group at multiple time points: week 4 (difference, − 1.21 [95% CI, -2.38 to -0.04; $P = 0.042$]), week 8 (difference, − 1.41 [95% CI, -2.81 to -0.02; $P = 0.047$]), and week 12 (difference, − 1.46 [95% CI, -2.89

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to -0.04; $P=0.044$]). Adverse events were reported in 3 of 80 patients (3.75%) in the Wuling capsule group and 3 of 80 patients (3.75%) in the control group ($P=1$), indicating no significant difference.

Conclusion This randomized clinical trial demonstrated that treatment with Wuling capsule over a 12-week period effectively reduced HAMD score in patients with mild depression associated with PD and the treatment was well tolerated.

Trial registration Chinese Clinical Trial Registry; registration number: ChiCTR2100046195; prospectively registered on May 9th, 2021.

Keywords Parkinson's disease, Wuling capsule, Depression

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily affects middle-aged and elderly individuals, with movement disorders being the hallmark clinical feature [1]. However, a growing body of evidence indicates that non-motor symptoms, such as depression, anxiety, and constipation, are also highly prevalent among patients with PD and can significantly diminish their quality of life [2–4]. Depression is particularly notable, affecting approximately 50% of patients with PD, a rate that far exceeds that of the general population and individuals with other chronic conditions [5–7]. This phenomenon, often referred to as depression in Parkinson's disease (DPD), not only exacerbates the emotional burden experienced by patients but may also accelerate the progression of PD itself [8, 9].

While current antidepressant treatments for DPD demonstrate some efficacy, their long-term use can lead to adverse effects such as dizziness, orthostatic hypotension, and drowsiness, which can negatively impact patients' neurological function [10]. Therefore, there is an urgent need to identify alternative therapeutic options that can effectively alleviate depressive symptoms while ensuring patient safety.

The Wuling capsule, a traditional Chinese medicine derived from mycelia of the rare fungus Xylaria nigripes (Kl.) Sacc. High-performance liquid chromatography (HPLC) analysis reveals that Wuling capsule contains a variety of bioactive constituents, including glycosides, adenosine, and amino acids. Notable compounds found in Wuling capsule includes 5-hydroxmellenin, 5-carboxylmellein, genistein, and 5-methylmellein. It is believed that the therapeutic effects of Wuling capsule arises from the synergistic interaction of these multiple components rather than the action of any single compound. This complexity underscores the holistic approach of traditional Chinese medicine, where the combined effects of various constituents may enhance overall efficacy [11]. Previous research has demonstrated that Wuling capsule exhibits both antianxiety and antidepressant effects in patients [12]. Additionally, studies have indicated that this formulation enhances brain uptake of glutamic acid and gamma-aminobutyric acid (GABA), while also increasing the activity of glutamate decarboxylase. This biochemical activity contributes to an elevated synthesis of GABA, an inhibitory neurotransmitter, in the cerebral cortex, thereby promoting central sedation and regulating central nervous function [13]. In addition, animal experiments have also confirmed the improvement effect of Wuling capsule on depression. Tan found that Wuling could improve depressive symptoms in rats with chronic mild unpredictable stress, and the mechanism may involve the antidepressant effect of L-arginine-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signaling pathway [14]. Western blot and qRT-PCR showed that administration of Wuling fungus powder for 14 days could reduce the level of hippocampal endoplasmic reticulum stress, reduce unfolded protein response, and inhibit apoptosis, suggesting that it could effectively alleviate the endoplasmic reticulum stress caused by the failure model of social competition, promote the restoration of endoplasmic reticulum homeostasis, and protect the normal function of cells, thereby exerting antidepressant effects [15]. Another study found that in a learned helpless mouse model, Wuling prevented depressive behavior by improving transporter-mediated mitochondrial phagocytosis [16].

Moreover, earlier clinical trials involving patients with PD have suggested that Wuling capsule may have beneficial effects on mood-related issues [17]. Despite these promising findings, there is a lack of comprehensive studies specifically evaluating the impact of Wuling capsule on depressive symptoms in PD through randomized controlled trials (RCTs). Consequently, this RCT aims to test the hypothesis that Wuling capsule is more effective than a placebo in reducing clinically significant depressive symptoms in patients with PD.

Methods

Study design

This randomized, double-blind, placebo-controlled trial was conducted from December 2021 to March 2024 across five clinical sites: Xinhua Hospital affiliated with Shanghai Jiao Tong University School of Medicine, Shanghai Municipal Hospital of Traditional Chinese Medicine affiliated with Shanghai University of

Traditional Chinese Medicine, Shanghai East Hospital, Shanghai Pudong New Area People's Hospital, and The Fourth Division Hospital of Xinjiang Production and Construction Corps. The clinical study was registered under ChiCTR2100046195 and follows the ethical principles outlined in the Declaration of Helsinki as well as the Good Clinical Practice (GCP) Guidelines. The detailed study protocol and statistical analysis plan are accessible within the methods section of the publication. A Data Safety Monitoring Board (DSMB), comprising clinicians and biostatisticians, oversaw the clinical trial, focusing particularly on participant safety and the completeness of the collected data, including the monitoring of adverse events.

Prior to the initiation of the study, ethical approval was obtained from the respective Ethics Committees at all participating sites. Informed consent was secured from all participants before any study-related procedures commenced, ensuring that each individual was fully informed about the study's objectives, methods, potential risks, and benefits. This rigorous adherence to ethical standards not only highlights our commitment to participant welfare but also reinforces the integrity of the research process. Such thorough measures are essential for fostering trust and transparency in clinical research.

Study population

This study aimed to enroll 160 participants diagnosed with early-stage PD accompanied by mild depression from multiple clinical sites. Inclusion criteria for participation were as follows: (1) a confirmed diagnosis of idiopathic PD in accordance with the Movement Disorder Society Clinical Diagnostic Criteria [18]; (2) age between 45 and 80 years; (3) a Hoehn and Yahr (H&Y) scale score indicating stages 1–2 [19]; (4) the presence of mild depression, defined as a HAMD score ranging from 8 to 17 [20]; (5) preserved cognitive function; (6) provision of written informed consent prior to randomization; and (7) stable use of levodopa and any concomitant anti-Parkinsonian medications for at least 30 days before enrollment. Exclusion criteria were as follows: (1) secondary Parkinsonism resulting from conditions such as traumatic brain injury or cerebrovascular accidents, or the use of medications such as antipsychotics; (2) other extrapyramidal disorders or significant cognitive impairment; (3) a diagnosis of schizophrenia, major depression, or any form of cognitive dysfunction; (4) prior use of any antidepressants or antipsychotics; (5) a history of suicidal thoughts or behaviors; (6) participation in other clinical trials; and (7) women who were pregnant or lactating. This careful selection process was designed to ensure a homogeneous study population, thereby enhancing the reliability and validity of the trial outcomes.

Patients with PD are classified into tremor dominant (TD), postural instability/gait difficulty (PIGD), and indeterminate according to the MDS-UPDRS score. The total score of the TD category item was calculated from the MDS-UPDRS score of 2.10, 3.15–3.18, and the total score of the PIGD category item was calculated from the MDS-UPDRS score of 2.12, 2.13, 3.10–3.12, and the patient was considered TD when the total score of the TD item was divided by the total score of the PIGD item ≥ 1.15; Patients are considered to have PIGD when the total TD score is divided by the total score of the PIGD category ≤ 0.90; When the total TD score divided by the PIGD total score is between 0.90 and 1.15, the patient is considered indeterminate.

Randomization, blinding, and intervention

Randomization numbers were generated using the PLAN procedure in SAS software, version 9.4 (SAS Institute Inc.), which ensured robust statistical integrity throughout the trial. These randomization sequences were concealed and securely stored by an independent individual who had no involvement in the study, thereby minimizing the potential for bias. To enhance the methodological rigor of the trial, all participants, including investigators and sponsors, were blinded to group allocation. Additionally, data analysts remained unaware of group identities until the completion of the data analysis.

Participants were randomly assigned in a 1:1 ratio to either the Wuling capsule group or the placebo group. Both the Wuling capsule and the placebo were indistinguishable in terms of color, odor, taste, shape, texture, specifications, appearance, packaging, labeling, and identification. This careful design made it virtually impossible for participants to differentiate between the two, thereby maintaining the integrity of the blinding process throughout the study. Following the randomization procedure, participants were assigned to one of the two parallel groups and administered either the Wuling capsule or the placebo orally. The treatment regimen consisted of three tablets, each containing 0.33 g of either the active ingredient or placebo powder, taken three times daily over a duration of 12 weeks. This design allows for a comprehensive evaluation of the efficacy and safety of Wuling capsule in the treatment of mild depression in patients with PD, ensuring that the results are both reliable and clinically relevant.

Outcomes

The primary outcome of this study was the change in the total score on the HAMD from baseline to week 12. Secondary outcomes included the assessment of anxiety disorders, measured by the Hamilton Rating Scale for Anxiety (HAMA) [21]; as well as sleep problems evaluated using both the Parkinson's Disease Sleep Scale-2

(PDSS-2) [22] and the Pittsburgh Sleep Quality Index (PSQI) [23]. Additionally, disease-specific quality of life was measured using the Parkinson's Disease Quality of Life Questionnaire (PDQ-8) [24] with all secondary outcomes also assessed from baseline to week 12.

Safety assessments comprised several components: (1) a comprehensive physical examination that included monitoring of pulse rate, heart rate, and blood pressure; (2) relevant laboratory measurements; and (3) the documentation of any adverse events (AEs) that may arise during the trial. For each reported AE, details were collected regarding the type of symptom, onset time, duration, and any therapeutic measures undertaken. Furthermore, we evaluated the relationship between the drug and the reported AEs, categorizing them as positive, probable, possible, or unrelated, and assessed the severity of AEs as mild, moderate, or severe. This multi-faceted approach to outcome and safety assessment provides a thorough understanding of both the efficacy and safety profile of the Wuling capsule in treating mild depression in patients with PD.

Statistical analysis

Data analysis was performed using IBM SPSS version 25.0 software. Treatment efficacy was analyzed for the intention-to-treat (ITT) population and per-protocol (PP) population. To address missing data, we employed the last-observation-carried-forward (LOCF) strategy, which is a common method for maintaining data integrity in clinical trials.

Descriptive statistics were computed for demographic characteristics and trial outcomes at each time point. The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as median (interquartile range [IQR]), while categorical variables were reported as proportions and counts. Comparisons between groups were conducted using the Wilcoxon rank-sum test for continuous data, and the chi-square test for categorical data. All statistical tests were two-tailed, with a significance threshold set at 5%.

To analyze the differences between the two groups, we employed Generalized Estimating Equations (GEE) models, which account for within-subject correlation over time. The models included factors such as treatment group, time, and the interaction between treatment group and time, providing a comprehensive understanding of the treatment effects over the study duration. Subgroup analyses were performed for statistically different outcomes.

For safety assessments, we utilized a safety population that encompassed all subjects who received at least one treatment and had a documented safety profile. This approach ensures that safety evaluations are robust and reflective of the entire cohort exposed to the intervention. Overall, this rigorous statistical framework facilitates a thorough evaluation of both efficacy and safety outcomes in our study.

Results

Baseline characteristics

From December 2021 to March 2024, a total of 160 patients were assessed for eligibility and subsequently randomized to receive either the Wuling capsule ($n = 80$) or a placebo ($n = 80$). The median age of 70.5 (IQR,67.00–75.00) years and 77 (48.13%) were male. The treatment efficacy was analyzed for both the ITT population and the PP population. The ITT population consisted of 160 patients, with 80 participants in each group. Throughout the trial, a total of 14 participants (8.75%) dropped out: 9 (11.25%) from the Wuling capsule group and 5 (6.25%) from the placebo group. Detailed information regarding trial procedures is illustrated in Fig. 1. Notably, there were no instances of emergency unblinding related to drug distribution during the study.

Demographic and clinical characteristics of the participants in both groups within the ITT population are summarized in Table 1. The efficacy analysis for the PP population is presented in Table S1. Importantly, there were no significant differences in clinical and demographic characteristics between the Wuling capsule and placebo groups at baseline, indicating that randomization was successful and that the two groups were comparable prior to treatment initiation. This balanced distribution of characteristics supported the validity of subsequent efficacy evaluations.

Efficacy outcomes

The results of the primary efficacy outcome analysis are shown in Table 2; Fig. 2. The Wuling capsule group exhibited markedly greater improvement in depressive symptoms compared to the placebo group, with the following results: week 4: difference = – 1.21 (95% CI, -2.38 to -0.04; $P = 0.042$); week 8: difference = – 1.41 (95% CI, -2.81 to -0.02; $P = 0.047$); and week 12: difference = – 1.46 (95% CI, -2.89 to -0.04; $P = 0.044$). In contrast, the placebo group showed no significant improvement in depressive symptoms across the assessed time points.

The results of analyses for the secondary outcomes are shown in Table 2. The Wuling capsule group experienced a notable reduction in PSQI score at week 8 (β, – 1.30 [95% CI, -2.55 to -0.05; $P = 0.042$]), but there was no difference at week 12. Besides, no significant differences were observed between the Wuling capsule and placebo groups regarding the HAMA score, PDQ-8 score, PDSS-2 score (Fig. 2). And Wuling capsule did not aggravate the MDS-UPDRS III score (Table S2). For a comprehensive view of the efficacy analysis within the

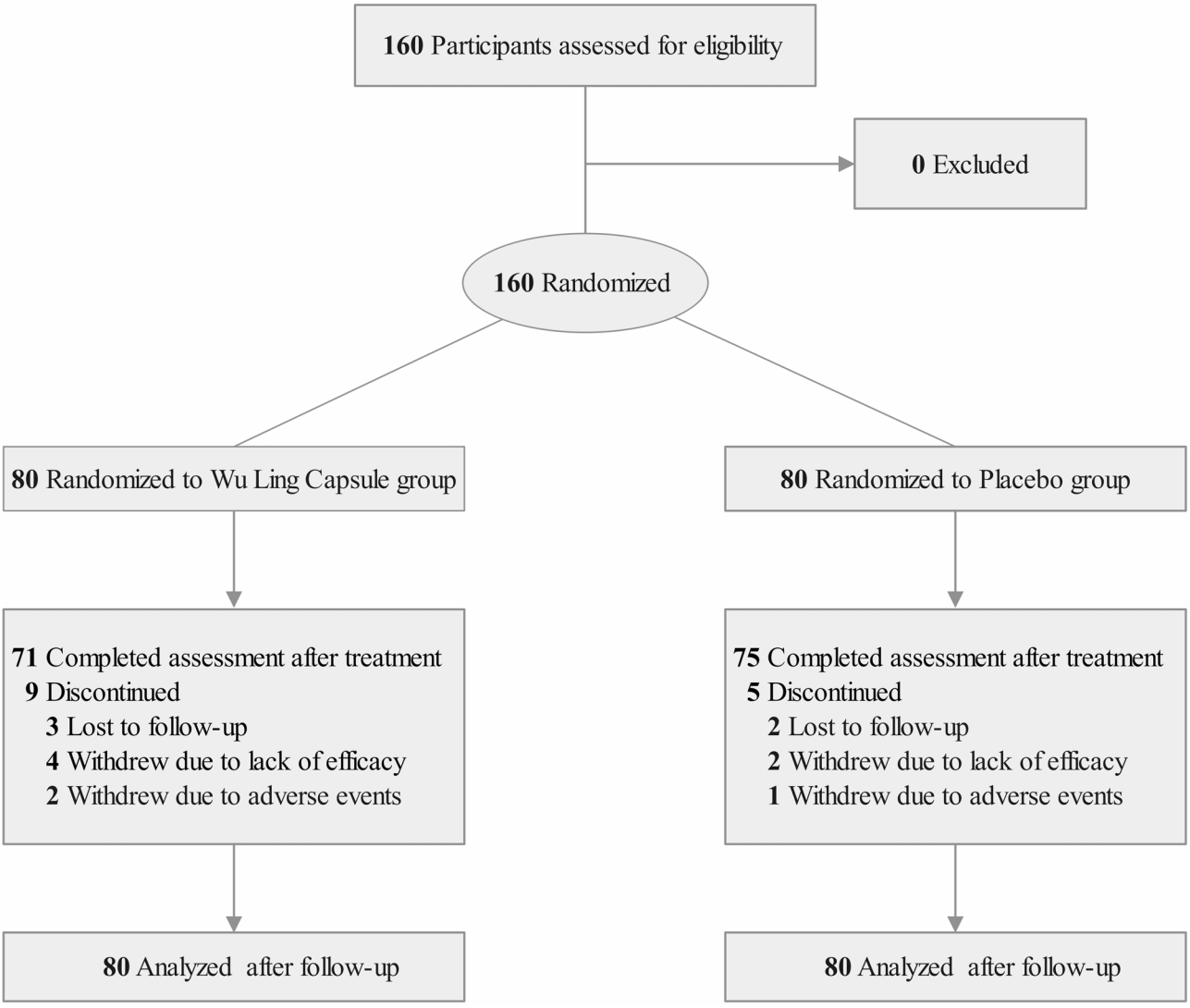

Fig. 1 Study flowchart

PP population, refer to Table S3, Table S4 and Figure S1. These findings indicate that the Wuling capsule significantly improves depressive symptoms among patients with PD and mild depression.

Additionally, the results of subgroup analysis showed that despite the clinical variability in patients with PD, the efficacy of Wuling Capsule was consistent across genders, baseline symptom severity, and PD subtypes, with no difference between subgroups, confirming its universal applicability. Details are shown in Fig. 3.

Safety outcome

All reported adverse events (AEs) during the study are detailed in Table 3. Notably, all AEs were classified as mild and transient in nature. There were no significant differences between the two groups in the occurrence of adverse events. Specifically, AEs were recorded in 3 out of 80 patients (1.25%) in the Wuling capsule group, and similarly, 3 out of 80 patients (1.25%) in the placebo group experienced AEs. Importantly, no serious adverse events were observed in either group throughout the duration of the trial. These findings suggest that the administration of Wuling capsule is associated with a favorable safety profile, comparable to that of the placebo, indicating that it is a well-tolerated option for patients with PD and mild depression.

Discussion

This multicenter, randomized, double-blind, placebo-controlled trial investigated the efficacy of the herbal medicine Wuling capsule in treating early PD accompanied by mild depression. In this study, we enrolled 160 patients across five clinical centers, and our results indicated that Wuling capsule significantly alleviated

Table 1 Baseline demographic and clinical characteristics of patients

Characteristic	Wuling Capsule group (*n* = 80)	Placebo group (*n* = 80)	*P* value
Age, year [median (IQR)]	70.00 (66.50–74.00)	71.00 (67.00–75.00)	0.722
Male, *n* (%)	37 (46.25%)	40 (50.00%)	0.635
BMI, kg/m^2[median (IQR)]	23.70 (22.00-24.95)	23.35 (21.40–24.80)	0.240
LEDD, mg[median (IQR)]	337.50 (187.50–525.00)	400.00 (300.00-540.50)	0.228
Pramipexole use at baseline, *n* (%)	44 (55.00%)	41 (51.25%)	0.340
Hoehn and Yahr score[median (IQR)]			0.566
1	19 (23.75%)	16 (20.00%)	
2	61 (76.25%)	64 (80.00%)	
MDS-UPDRS score[median (IQR)]			
Part I	9.00 (7.00–12.00)	11.00 (7.00–15.00)	0.078
Part II	9.00 (5.00–13.00)	11.00 (7.00–13.00)	0.142
Part III	21.00 (15.00–30.00)	23.50 (18.00–31.00)	0.172
Part IV	0.00 (0.00–0.00)	0.00 (0.00–1.00)	0.415
MMSE score[median (IQR)]	28.00 (26.00–29.00)	27.00 (26.00–29.00)	0.983
HAMD score[median (IQR)]	11.00 (9.00-13.50)	11.00 (10.00–14.00)	0.424
HAMA score[median (IQR)]	9.00 (6.00-12.50)	11.00 (8.00–16.00)	0.098
PDSS-2score[median (IQR)]	15.50 (10.50–21.50)	17.00 (12.00–25.00)	0.234
PSQI score[median (IQR)]	10.00 (7.00–13.00)	10.00 (6.00-13.50)	0.845
PDQ-8 score[median (IQR)]	6.50 (4.00–8.00)	6.00 (4.00–9.00)	0.529

BMI: body mass index; LEDD: levodopa equivalent daily dose; H&Y stage, Hoehn and Yahr stage; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDSS-2: Parkinson's Disease Sleep Scale2; PSQI, Pittsburgh Sleep Quality Index; PDQ-8: Parkinson's Disease Quality of Life; Questionnaire IQR, interquartile range

depressive symptoms while being generally well tolerated over the 12-week treatment period.

Despite the significant impact of depression on functional recovery and quality of life in patients with PD, this condition is frequently overlooked in clinical practice. A strikingly low number of patients receive a diagnosis, and even fewer are offered treatment. Current therapeutic options for depression in PD encompass pharmacotherapy, psychotherapy, and electroconvulsive therapy, with pharmacological treatment being the predominant approach. Antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRIs), are commonly utilized, may interact negatively with other PD treatments, particularly monoamine oxidase B (MAO-B) inhibitors [25, 26]. Moreover, dopamine receptor agonists, such as pramipexole, are linked to exacerbate extrapyramidal symptoms and other non-motor issues associated with PD. Consequently, there is a pressing need for effective medications that present minimal adverse effects, representing a significant advancement in managing PD with depression.

In recent years, traditional Chinese medicine (TCM) has gained recognition as a complementary and alternative therapy for its safety and efficacy in alleviating depressive symptoms. The Wuling capsule, primarily composed of Wuling mycelia derived from Xylaria species—a rare type of fungus—has been refined through modern bioengineering techniques. The bioactive constituents of Wuling mycelia include adenosine, adenine, uridine, guanosine, polysaccharides, mannitol, ergosterol, cholesterol, sitosterol, and a variety of amino acids, including nine that are essential for human health. Additionally, Wuling mycelia contains trace minerals and micronutrients such as iron, zinc, manganese, copper, phosphorus, magnesium, calcium, and germanium, as well as several vitamins including B1, B2, B6, E, A, D2, and K1. Overall, Wuling capsule appears to be more effective than placebo, and Wuling capsule does not worsen motor or non-motor function suggesting that they may serve as a valuable complementary option for patients suffering from DPD in our study. The therapeutic effects of Wuling capsule can be partially attributed to the diverse benefits of Wuling mycelia, a key component of the formulation. Rich in amino acids, vitamins, and essential micronutrients, Wuling mycelia has been shown in studies to facilitate the entry of glutamate (Glu) and gamma-aminobutyric acid (GABA) into the brain, thereby activating GABA receptors and influencing central nervous system function. The mechanism by which Wuling capsule exert their effects may involve enhancing GABA synthesis and promoting receptor activity in brain cells, in addition to increasing brain energy reserves and reducing energy expenditure [27]. This multifaceted action not only contributes to the antidepressant effects but also improves brain energy metabolism, facilitating the recovery of neuronal function in affected patients.

Previous studies have shown that Wuling capsule can improve insomnia, and although our results show no difference in sleep improvement between the Wuling capsule group and the control group at week 12, the Wuling capsule group has a better sleep improvement than the placebo group at week 8, and the PSQI score in the Wuling capsule group is lower than that of the placebo group at week 12, although the difference is not statistically significant, this may still suggest a trend that Wuling capsule can improve insomnia. There was no difference in sleep improvement between the Wuling capsule group and the control group at week 12 in this study, possibly since we did not specifically screen for pre-existing sleep disorders

Table 2 Generalized estimating equation analysis for the comparison of outcomes[a]

Outcome	Median (IQR)		Group Effectb		Time Effectc		Group*Time Effectd	
	Wuling Capsule	Placebo	β (95%CI)	*P* value	β (95%CI)	*P* value	β (95%CI)	*P* value
Primary								
HAMD score								
Week 0	11.00 (9.00-13.50)	11.00 (10.00–14.00)	-0.34 (-1.19 ~ 0.52)	0.439	N/A	N/A	N/A	N/A
Week 2	10.00 (9.00–12.00)	11.00 (9.00–13.00)			-0.79 (-1.37 to -0.21)	0.008	-0.25 (-1.08 to 0.58)	0.556
Week 4	9.00 (7.00–11.00)	10.00 (8.00–13.00)			-1.45 (-2.29 to -0.62)	<0.001	-1.21 (-2.38 to -0.04)	0.042
Week 8	8.00 (6.00–10.00)	9.50 (6.50–12.00)			-2.08 (-3.06 to -1.09)	<0.001	-1.41 (-2.81 to -0.02)	0.047
Week 12	8.00 (5.00–10.00)	9.50 (6.50–12.00)			-2.31 (-3.26 to -1.37)	<0.001	-1.46 (-2.89 to -0.04)	0.044
Secondary								
HAMA score								
Week 0	9.00 (6.00-12.50)	11.00 (8.00–16.00)	-1.30 (-3.43 ~ 0.83)	0.230	N/A	N/A	N/A	N/A
Week 2	9.00 (6.00–12.00)	10.00 (8.00–14.00)			-0.96 (-1.76 to -0.17)	0.018	0.45 (-1.13 to 2.03)	0.577
Week 4	8.00 (5.00–12.00)	9.50 (7.00–13.00)			-1.95 (-2.85 to -1.05)	<0.001	0.45 (-0.90 to 1.80)	0.514
Week 8	8.00 (4.00–11.00)	9.00 (4.50–12.50)			-2.83 (-3.95 to -1.71)	<0.001	0.45 (-1.26 to 2.16)	0.606
Week 12	8.00 (3.00–11.00)	9.00 (4.50–12.50)			-3.03 (-4.19 to -1.86)	<0.001	0.74 (-0.98 to 2.45)	0.399
PDSS-2 score								
Week 0	15.50 (10.50–21.50)	17.00 (12.00–25.00)	-1.60 (-4.25 ~ 1.05)	0.236	N/A	N/A	N/A	N/A
Week 2	15.00 (10.50–20.50)	14.50 (11.00-23.50)			-1.09 (-1.70 to -0.48)	<0.001	0.13 (-1.09 to 1.34)	0.840
Week 4	12.50 (9.00–19.00)	15.00 (10.50–23.50)			-1.66 (-2.55 to -0.78)	<0.001	-1.01 (-2.57 to 0.55)	0.203
Week 8	13.00 (7.00–18.00)	13.50 (9.50–21.00)			-2.71 (-3.71 to -1.71)	<0.001	-0.05 (-1.56 to 1.46)	0.948
Week 12	12.00 (7.00–18.00)	12.50 (8.00-21.50)			-3.78 (-4.97 to -2.59)	<0.001	0.23 (-1.56 to 2.01)	0.804
PSQI score								
Week 0	10.00 (7.00–13.00)	10.00 (6.00-13.50)	-0.20 (-1.58 ~ 1.18)	0.777	N/A	N/A	N/A	N/A
Week 2	9.00 (6.000–12.00)	10.00 (6.00-13.50)			-0.11 (-0.67 to 0.45)	0.693	-0.43 (-1.10 to 0.25)	0.216
Week 4	8.50 (5.50–11.00)	9.00 (6.00–13.00)			-0.55 (-1.30 to 0.20)	0.149	-0.94 (-1.91 to 0.04)	0.059
Week 8	7.50 (5.00–10.00)	9.00 (6.00–13.00)			-0.76 (-1.77 to 0.24)	0.137	-1.30 (-2.55 to -0.05)	0.042
Week 12	7.00 (4.50–11.00)	8.00 (5.00–12.00)			-1.48 (-2.30 to -0.65)	<0.001	-0.75 (-1.82 to 0.32)	0.168
PDQ-8 score								
Week 0	6.50 (4.00–8.00)	6.00 (4.00–9.00)	-0.19 (-1.34 ~ 0.97)	0.750	N/A	N/A	N/A	N/A
Week 2	6.00 (4.00–8.00)	6.00 (4.00–8.00)			-0.46 (-0.99 to 0.07)	0.087	0.01 (-0.69 to 0.72)	0.972
Week 4	6.00 (3.50-8.00)	5.00 (3.50-8.00)			-0.69 (-1.15 to -0.23)	0.003	-0.11 (-0.75 to 0.53)	0.731
Week 8	5.00 (3.00–8.00)	4.00 (3.00–7.00)			-1.31 (-1.86 to -0.76)	<0.001	0.19 (-0.52 to 0.90)	0.605
Week 12	5.50 (3.00–8.00)	4.00 (2.00–7.00)			-1.24 (-1.82 to -0.66)	<0.001	0.20 (-0.59 to 0.99)	0.618

HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDQ-8: Parkinson's Disease Quality of Life Questionnaire; PDSS-2: Parkinson's Disease Sleep Scale2; PSQI, Pittsburgh Sleep Quality Index

[a] The placebo group and the baseline measurement (Week 0) were the reference categories in the generalized estimating equation model and its corresponding null variables

[b] Group effect was defined as group differences at baseline between Wuling Capsule group and placebo group

[c] Time effect at Week 2 defined as change of scores for placebo group at Week 2 compared with Week 0; Week 4 defined as change of scores for placebo group at Week 4 compared with Week 0; Week 8 defined as change of scores for placebo group at Week 8 compared with Week 0; Week 12 defined as change of scores for placebo group at Week 12 compared with Week 0

[d] Group × time effect at Week 2 defined as additional change of scores for Wuling Capsule group compared with placebo group at Week 2; Week 4 defined as additional change of scores for Wuling Capsule group compared with placebo group at Week 4; Week 8 defined as additional change of scores for Wuling Capsule group compared with placebo group at Week 8; Week 12 defined as additional change of scores for Wuling Capsule group compared with placebo group at Week 12

during participant enrollment. At baseline, both groups exhibited relatively low PDSS-2 and PSQI scores, indicating that participants had fairly good sleep quality. Therefore, although Wuling may improve sleep, its effect may not be significant. Small sample size, difficulty in detecting subtle changes and potential mismatches between Western-derived outcome scales and TCM's holistic therapeutic mechanisms may limit the possibility of testing.

In terms of safety outcomes, the incidence of adverse events was low across both groups, with all reported AEs being mild and transient. No significant differences in AEs were observed between the two groups, aligning with previous reports on the safety of Wuling capsule. Only three minor adverse events were recorded in the Wuling group, further supporting the notion that the Wuling capsule is a safe therapeutic option for managing depression in patients with PD. Therefore, we recommend the use of Wuling capsule in patients with early PD and depression.

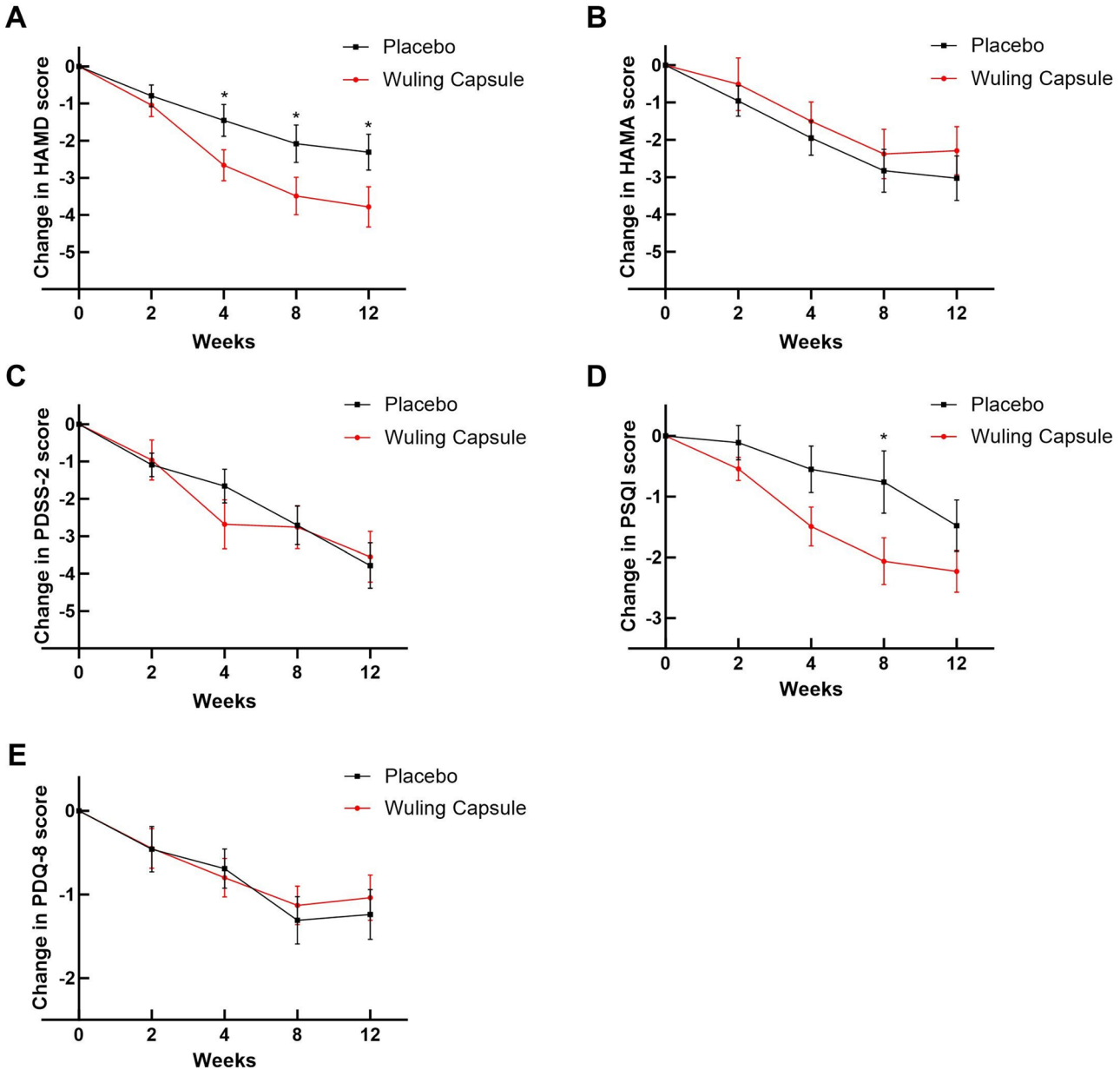

Fig. 2 Therapeutic effects over time in the intention-to-treat population. HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; PDSS-2: Parkinson's Disease Sleep Scale2; PSQI, Pittsburgh Sleep Quality Index; PDQ-8: Parkinson's Disease Quality of Life; Error bars represent standard error of the mean

Limitations

Our trial has some limitations. First, we expected to include PD patients with mild depression with baseline HAMD score ranging from 8 to 17, but most of the included patients had very mild depression (median baseline HAMD score of 11 in both groups), resulting in patients with severe depression were not included. It is impossible to draw a conclusion on whether Wuling capsule is effective for moderate to severe depression in PD. Second, the sample sizes in our analyses tended to be small, so the results must be interpreted cautiously. Additionally, this trial was mainly conducted in China, and the findings may not be easily generalizable to other populations. Furthermore, the study duration of 12 weeks restricts our ability to infer long-term effects, which may limit the broader applicability of our results to a larger population of PD patients. To address these issues, in the future, we will strive to conduct multi-national trials to explore racial and regional differences in treatment response to Wuling capsule, as well as long-term follow-up studies (≥ 1 year) to evaluate ongoing clinical efficacy and safety profiles.

Variables	n (%)	Placebo	Wuling Capsule	β (95%CI)	P
		Mean ± SD			
All patients	160 (100.00)	-2.45 ± 4.05	-3.66 ± 4.88	-1.21 (-2.60 ~ 0.18)	0.089
Sex					
Female	83 (51.88)	-1.85 ± 3.71	-3.33 ± 5.54	-1.48 (-3.52 ~ 0.57)	0.161
Male	77 (48.12)	-3.05 ± 4.32	-4.05 ± 4.01	-1.00 (-2.87 ~ 0.86)	0.295
Subtype					
Indeterminate	7 (4.38)	-0.25 ± 5.56	-6.67 ± 2.31	-6.42 (-13.22 ~ 0.39)	0.124
PIGD	56 (35.00)	-1.91 ± 4.53	-2.76 ± 3.24	-0.85 (-3.07 ~ 1.37)	0.457
TD	97 (60.62)	-3.12 ± 3.37	-3.84 ± 5.42	-0.72 (-2.60 ~ 1.16)	0.456
HY					
1	35 (21.88)	-2.19 ± 3.95	-2.63 ± 4.11	-0.44 (-3.13 ~ 2.24)	0.748
2	125 (78.12)	-2.52 ± 4.10	-3.98 ± 5.08	-1.47 (-3.08 ~ 0.15)	0.077

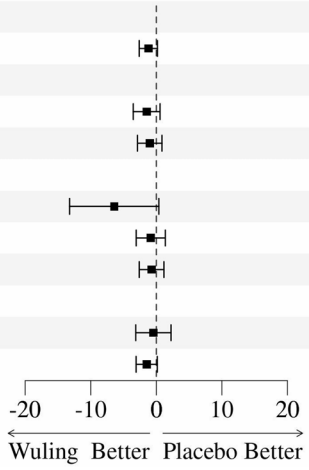

Fig. 3 Primary outcome in prespecified subgroups

Table 3 Adverse events

Event	Wuling Capsule (*n* = 80)	Placebo (*n* = 80)	*p* value
Diarrhea, *n* (%)	1.00 (1.25%)	1.00 (1.25%)	1.00
Nausea, *n* (%)	1.00 (1.25%)	1.00 (1.25%)	1.00
Headache, *n* (%)	1.00 (1.25%)	1.00 (1.25%)	1.00

Conclusion

In conclusion, this study demonstrates that a 12-week treatment with Wuling capsule effectively reduces HAMD score and is well tolerated among patients with early PD and mild depression. Our findings support the efficacy and safety of Wuling capsule as a complementary treatment option for enhancing the management of depression in PD. Future research should further explore the long-term effects and potential interactions of the Wuling capsule within broader treatment paradigms for PD, contributing to a more comprehensive understanding of its role in clinical practice.

Abbreviations

PD	Parkinson's disease
DPD	Depression in Parkinson's disease
GABA	Gamma-aminobutyric acid
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
H&Y	Hoehn and Yahr
MoCA	Montreal Cognitive Assessment
HAMA	Hamilton Rating Scale for Anxiety
HAMD	Hamilton Depression Scale
PDSS-2	Parkinson's Disease Sleep Scale-2
PSQI	Pittsburgh Sleep Quality Index
PDQ-8	Parkinson's Disease Quality of Life Questionnaire
TD	Tremor dominant
PIGD	Postural instability/gait difficulty
TCM	Traditional Chinese medicine
AEs	Adverse events

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12906-025-04991-y.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Acknowledgements

Not applicable.

Author contributions

ZGL, XHZ designed the study. YWZ, LL, DYH, WTL, QYZ, HQL, RX, MJL, JG, NW, ZHL, XHZ, XXC, SZZ, HNF, JFL, XDC performed the study. YWZ, LL analyzed the data. YWZ, YZ wrote the manuscript. ZGL, YZ revised the manuscript. All authors read and approved the final manuscript. The manuscript has not been submitted or published in other journals.

Funding

This study was supported by the Projects of National Science Foundation of China (81974173, 82271274, 82171242, 82471260, 82474606), Shanghai Demonstration Project of Cooperative Diagnosis and Treatment for Major Difficult Diseases with integrated modern and traditional Chinese medicine [ZY(2021–2023)-0207-01-03], Innovative research team of high-level local universities in Shanghai(SHSMU-ZDCX20211901), Projects of the Shanghai Committee of Science and Technology (22Y11904100), Medical Engineering Cross Research Fund of Shanghai Jiao Tong University(YG2023ZD12), Medical Engineering Cross Research Fund of University of Shanghai for Science and Technology(2023GD-XH06Z).

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, the Ethics

Committee of Shanghai Hospital of Traditional Chinese Medicine affiliated to Shanghai University of Traditional Chinese Medicine, the Ethics Committee of Shanghai East Hospital, the Ethics Committee of Shanghai Pudong New Area People's Hospital, and the Ethics Committee of the Fourth Division Hospital of Xinjiang Production and Construction Corps, and informed consent has been obtained from participants. This study is in line with the Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

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Received: 7 February 2025 / Accepted: 24 June 2025
Published online: 09 July 2025

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