

Review Article

Clinical effect of donepezil hydrochloride in the treatment of Parkinson's disease patients: a meta-analysis

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Abstract: Objective: To evaluate the therapeutic effectiveness of donepezil hydrochloride in patients with Parkinson's disease (PD) and inform subsequent management strategies. Methods: We systematically reviewed randomized and non-randomized studies on donepezil hydrochloride in PD patients, retrieved from PubMed, Web of Science, Embase, and the Cochrane Library, covering data from inception to March 2025. Meta-analysis was performed using RevMan 5.4 software. Results: Ten eligible studies were included. The meta-analysis revealed significant improvements in Mini-Mental State Examination (MMSE) scores in the treatment group compared to controls (SMD = 1.67, 95% CI [0.81, 2.54], $P < 0.0001$). The Unified Parkinson's Disease Rating Scale (UPDRS) scores were significantly reduced (SMD = -2.79, 95% CI: -4.85 to -0.74, $P = 0.008$), as were Clinician's Interview-Based Impression of Change (CIBIC+) scores (SMD = -0.27, 95% CI: -0.45 to -0.08, $P = 0.004$). Subgroup analysis indicated consistent improvements in MMSE scores across different subgroups, with significant differences observed. Heterogeneity was found in the age subgroup but not in the disease duration subgroup (< 3 years). Adverse events occurred in 42.07% (374/889) of the treatment group, with no heterogeneity across studies ($I^2 = 0\%$) and a statistically significant increase in risk (RR = 1.46, 95% CI [1.15, 1.84], $P = 0.002$). Conclusion: The meta-analysis suggests that donepezil hydrochloride provides cognitive benefits for PD patients. However, the higher incidence of adverse reactions warrants careful consideration of the benefits and risks when using donepezil in clinical practice.

Keywords: Donepezil hydrochloride, clinical efficacy, Parkinson's disease, meta-analysis

Introduction

Parkinson's disease (PD) is the second most prevalent chronic neurodegenerative disorder, after Alzheimer's disease, primarily affecting middle-aged and older adults [1]. Epidemiological studies show that the prevalence of PD among individuals aged 65 and above in China is 1.7%, with projections indicating that the number of PD patients in China will reach 5 million by 2030 [2, 3]. Although the exact cause of PD remains unclear, most research suggests it results from the loss of dopamine-producing neurons in the substantia nigra. Patients with PD typically present with executive dysfunction, reduced attention, impaired visuospatial abilities, and memory decline [4, 5]. As the disease progresses, dementia may develop, leading to a significant decline in cognitive function, which severely affects physical health, daily activities,

and places a considerable burden on families and society [6].

Currently, pharmacotherapy is the primary treatment for PD [7]. Clinical evidence indicates that anti-Parkinsonian medications can effectively manage symptoms, slow disease progression, and improve patients' quality of life [8]. Donepezil hydrochloride, a selective acetylcholinesterase inhibitor, enhances cognitive function by inhibiting acetylcholine hydrolysis and increasing its levels in the brain. It has been widely used in PD management and shows certain clinical benefits [9]. Despite numerous randomized controlled trials investigating donepezil hydrochloride for PD, a comprehensive understanding of its therapeutic effects remains lacking. Furthermore, the results of these studies are inconsistent, and a systematic evaluation is absent. Therefore, this

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Table 1. PubMed database retrieval strategy

Steps	Term
#1	("Parkinson Disease"[MeSH Terms] OR Idiopathic Parkinson's Disease* OR Idiopathic Parkinson Disease* OR Lewy Body Parkinson Disease* OR Lewy Body Parkinson's Disease* OR Paralysis Agitans* OR Parkinson's Disease* OR Parkinson Disease, Idiopathic* OR Parkinson's Disease, Idiopathic* OR Parkinson's Disease, Lewy Body* OR Primary Parkinsonism* OR Parkinsonism, Primary*)
#2	("Donepezil" [MeSH Terms] OR Donepezil Hydrochloride OR "1-Benzyl-4-((5,6-dimethoxy-1-indanon)-2-yl)methylpiperidine hydrochloride" OR "Aricept" OR "E 2020" OR "E-2020" OR "E2020" OR "Erantz" OR "Donepezilium Oxalate Trihydrate")
#3	(efficacy OR effectiveness OR safety OR "side effects" OR "adverse events")
#4	#1 AND #2 AND #3 AND

research aims to conduct a meta-analysis to thoroughly assess the clinical efficacy and safety of donepezil hydrochloride in PD management, providing more reliable, evidence-based insights for clinical practice.

Materials and methods

This study has been registered with PROSPERO (CRD420251025145).

Literature search methods

We conducted a computerized search of articles published in PubMed, Embase, and the Cochrane Library databases that met the criteria for evaluating the clinical effects of donepezil hydrochloride in treating PD. The search terms included "Donepezil", "Donepezil Hydrochloride", "Parkinson's Disease", "Idiopathic Parkinson's Disease", and "Lewy Body Parkinson's Disease". A search strategy combining subject headings and free-text terms was employed and adjusted for each database. To ensure a comprehensive search, we also reviewed the reference lists of the original studies. Searches covered all available data from the inception of each database through March 2025. The search strategy used for PubMed is detailed in **Table 1**.

Inclusion and exclusion criteria

Inclusion criteria: (1) Randomized controlled trials (RCTs) or non-RCT studies published in English. (2) Patients diagnosed with Parkinson's disease (PD), with no other restrictions. (3) Patients receiving conventional treatment, placebo, or other medications as the control group. (4) Treatment group receiving donepezil hydrochloride in addition to the control group's treatment. (5) Studies reporting at least one

outcome measure. Exclusion criteria: (1) Duplicate publications. (2) Studies for which the full text could not be obtained. (3) Review articles. (4) Case reports, treatment summaries. (5) Trials that did not clearly specify donepezil as part of the intervention. (6) Studies primarily based on personal experience, expert opinion, or animal experiments.

Outcome measures

The primary outcomes were the Mini-Mental State Examination (MMSE) scores, Unified Parkinson's Disease Rating Scale (UPDRS) scores, and adverse reactions following drug administration. Secondary outcomes included CIBIC+ scores, Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) scores, and Neuropsychiatric Inventory (NPI) scores (NPI-2 = hallucinations + cognitive fluctuations).

Literature screening and data extraction

Following the methodologies outlined in the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA guidelines, two researchers (Min Zhu and Chong Liang) independently conducted the literature screening. Duplicates were removed using EndNote X9, after which each investigator independently applied the inclusion and exclusion criteria, and cross-verified the selected records. Disagreements were resolved by consulting a third researcher (Jinbiao Qin). Missing data were requested from the authors of the original studies. For eligible studies, the following data were extracted: (1) first author, publication year; (2) interventions and duration of treatment for both the treatment and control groups; (3) outcome evaluation metrics; (4) age; (5) disease duration.

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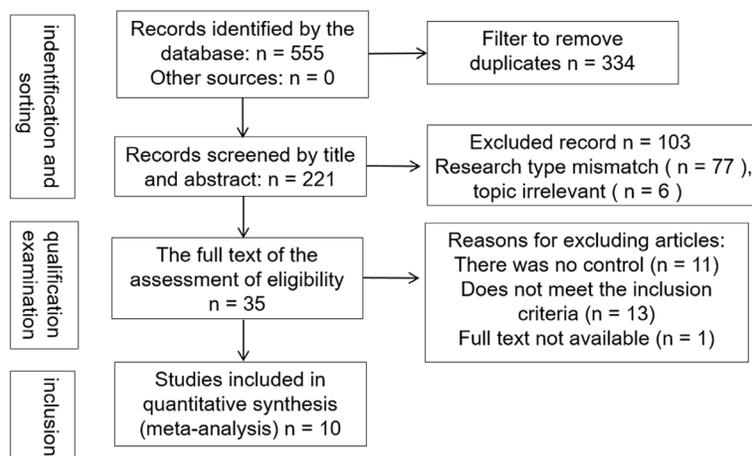


Figure 1. Screening process.

Risk of bias assessment

The risk of bias in the included studies was assessed using the Cochrane Collaboration's Risk of Bias Tool for RCTs [12]. This assessment evaluated random sequence generation, allocation concealment, blinding of participants and staff, completeness of outcome data, selective reporting, and other potential sources of bias. Two researchers (Chong Liang and Wei Feng) independently performed the risk of bias assessment, and disagreements were resolved by consulting a third researcher (Min Zhu).

Statistical analysis

Meta-analysis was conducted using RevMan 5.4 software. Heterogeneity among studies was assessed using the I^2 statistic. If $P \geq 0.1$ and $I^2 \leq 50\%$, indicating low heterogeneity, a fixed-effect model was applied. If $P < 0.1$ and $I^2 > 50\%$, indicating significant heterogeneity, studies were sequentially excluded to identify sources of heterogeneity. Subgroup analysis was performed if necessary, and after excluding heterogeneity, a random-effects model was used. For categorical outcomes, relative risk (RR) was used as the effect size measure, while mean difference (MD) was used for continuous outcomes. All effect size measures were reported with 95% confidence intervals (CIs), and P -values < 0.05 were considered statistically significant. Publication bias was assessed by examining the symmetry of funnel plots, and the meta-analysis outcomes were visually represented using forest plots.

Results

Literature search results and basic information

An initial search identified 221 articles. After reviewing the titles and abstracts, 81 articles were excluded for not meeting the content criteria. A full-text search was conducted for 35 articles, resulting in the exclusion of 25 studies: one article was unavailable in full text, 11 lacked a control group, and 13 did not meet the inclusion criteria. Ultimately, 10 studies [11-20] were included in the meta-analysis. The screening process is outlined in **Figure 1**.

Features of the studies included

The review included 10 studies, summarized in **Table 2**. The studies involved 1,530 patients, with 957 in the treatment group and 573 in the control group. Treatment duration ranged from 10 weeks to 208 weeks, with most studies using a 12-week duration. At least one outcome indicator was reported in all studies, with a maximum of six outcome indicators described.

Quality assessment

The quality of the 10 RCTs was assessed using the Cochrane risk of bias tool. Each item was rated as "low risk of bias", "unclear", or "high risk of bias". The risk of bias assessment is presented in **Figure 2**. Of the included studies, 8 clearly described the random sequence generation (low bias), 7 were double-blinded (low bias), and 9 had complete data (low bias), suggesting overall reliable quality.

Meta-analysis results

MMSE scores: All 9 studies reported the effect of donepezil on MMSE scores. Significant variability was observed across the studies ($P < 0.05$, $I^2 = 74\%$), so a random-effects model was used. The meta-analysis showed that after donepezil intervention, MMSE scores in the treatment group were significantly higher

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Table 2. Characteristics of included studies

Eligible studies	Block mode	Intervention measures		Course of treatment	Sample size (effective number/total number)		Adverse reactions		Age (years)		Course (years)		Index
		Treatment group	Control group		Treatment group	Control group	Treatment group	Control group	Treatment group	Control group	Treatment group	Control group	
Aarsland 2002 [11]	random	Donepezil	placebo	10 weeks	6/14	6/12	10	9	NA		NA		(1), (3), (4), (15)
Dubois 2012 [12]	random	5 mg Donepezil	placebo	24 weeks	183/195	170/173	27	19	72.0±6.83	72.9±6.48	7.8±5.41	7.9±5.30	(1), (3), (5), (6), (7), (8), (15)
Leroi 2004 [13]	random	10 mg Donepezil	placebo	24 weeks	173/182	170/173	30	19	70.8±7.46	72.9±6.48	9.2±5.71	7.9±5.30	(1), (9), (15)
Ravina 2005 [14]	random	Donepezil	placebo	18 weeks	7/7	9/9	5	4	66.20±9.30	70.80±11.80	11.0±5.90	6.40±2.80	(1), (9), (15)
Sawada 2018 [15]	random	Donepezil	placebo	26 weeks	9/21	10/20	11	9	75.0±9.8	72.1±8.1	7.1±2.6	14.4±13.1	(1), (5), (10), (11), (15)
Mori 2024 [16]	random	Donepezil	placebo	48 weeks	72/72	73/73	39	36	67.2±7.3	69.0±7.0	8.2±4.8	7.8±4.3	(1), (13), (14), (15)
Mori 2024 [16]	random	Donepezil+placebo	placebo	12 weeks	75/81	76/79	24	12	78.0 (6.44)	77.6 (7.15)	2.15 (1.96)	2.34 (1.88)	(1), (12), (16)
Baba 2022 [17]	random	Donepezil	placebo	208 weeks	103/103	98/98	81	63	67.9±4.6	67.9±4.9	6.9±4.4	6.7±4.1	(15)
Ikeda 2015 [18]	random	5 mg Donepezil+placebo	placebo	12 weeks	32/33	32/34	30	31	78.8±5.1	77.2±6.1	2.7±1.8	2.0±2.3	(1), (12), (15), (16)
	random	10 mg Donepezil+placebo	placebo	12 weeks	43/49	31/46	34	31	77.7±6.8	77.2±6.1	2.3±1.9	2.0±2.3	
Mori 2012 [19]	random	5 mg Donepezil+placebo	placebo	12 weeks	32/33	32/34	27	24	77.9±6.8	78.6±4.7	NA		(1), (4), (12), (15), (16)
	random	3 mg Donepezil+placebo	placebo	12 weeks	35/35	32/34	32	24	79.6±4.5	78.6±4.7			
	random	10 mg Donepezil+placebo	placebo	12 weeks	37/36	32/34	24	24	78.6 ±6.1	78.6±4.7			
Baik 2021 [20]	non randomized	Donepezil+placebo	placebo	48 weeks	20/21	29/29		NA	69.1±7.1	66.7±7.1	5.9±5.1	3.6±4.4	(1), (4)

Notes: (1) MMSE: Mini-Mental State Examination; (2) MoCA: Montreal Cognitive Assessment; (3) CIBIC+: Clinician's Interview-Based Impression of Change; (4) UPDRS: Unified Parkinson's Disease Rating Scale; (5) ADAS-cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; (6) D-KEFS Verbal Fluency: Delis-Kaplan Executive Function System Verbal Fluency; (7) BTA: Brief Test of Attention; (8) DAD: Dementia Disability Assessment Scale; (9) DRS: Dementia Rating Scale; (10) MDRS: Mattis Dementia Rating Scale; (11) CGI: Clinical Global Impression scale; (12) NPI-2: Neuropsychiatric Inventory-2; (13) WMS: Wechsler Memory Scale; (14) PPQ: Parkinson Psychosis Questionnaire; (15) Adverse events; (16) NPI-10: Neuropsychiatric Inventory-10.

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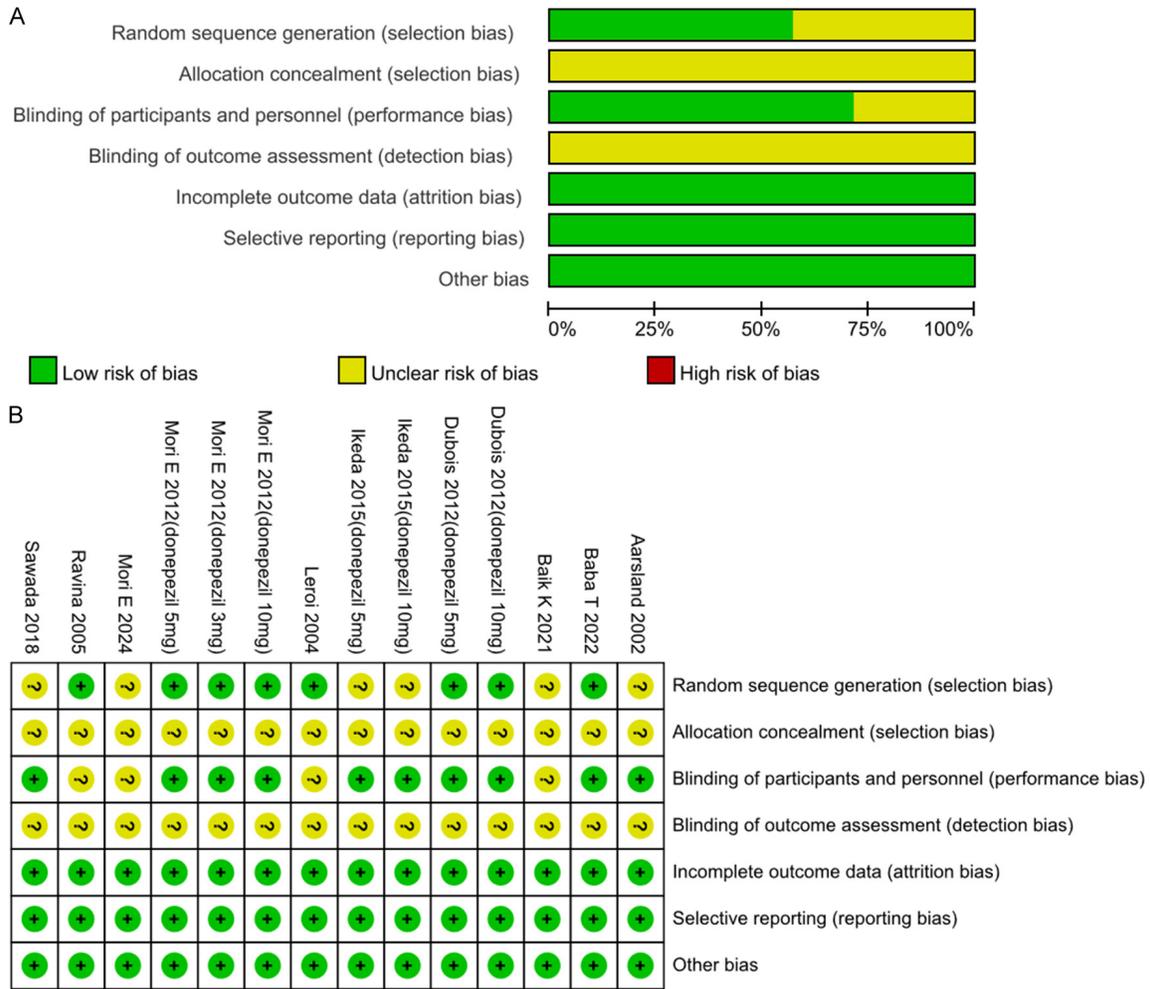


Figure 2. Risk of Bias Assessment Results for Included Studies. Notes: (A) Risk of bias assessment results for included studies; (B) Summary of risk of bias for included studies.

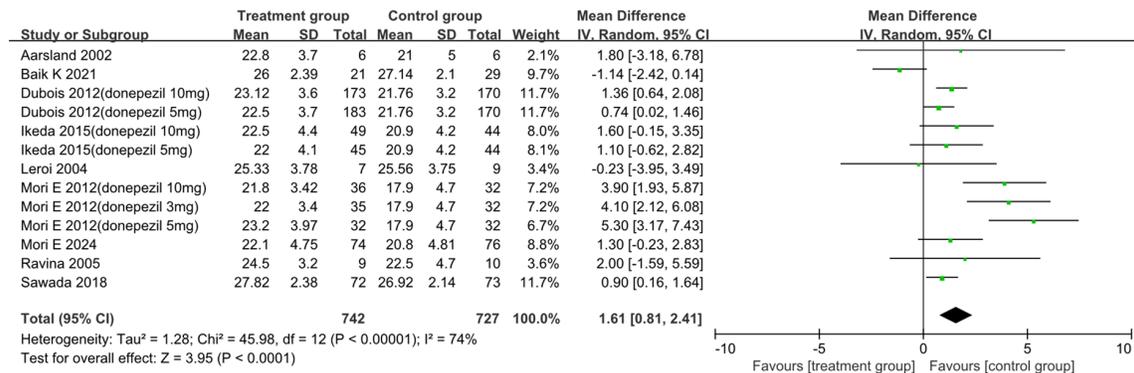


Figure 3. Meta-analysis of MMSE scores between the two groups.

than in the control group (SMD = 1.61, 95% CI [0.81, 2.41], P < 0.05), as shown in **Figure 3**.

Subgroup analyses based on the average age of patients (> 70 years or ≤ 70 years) are displayed in **Figure 4**. Heterogeneity was present

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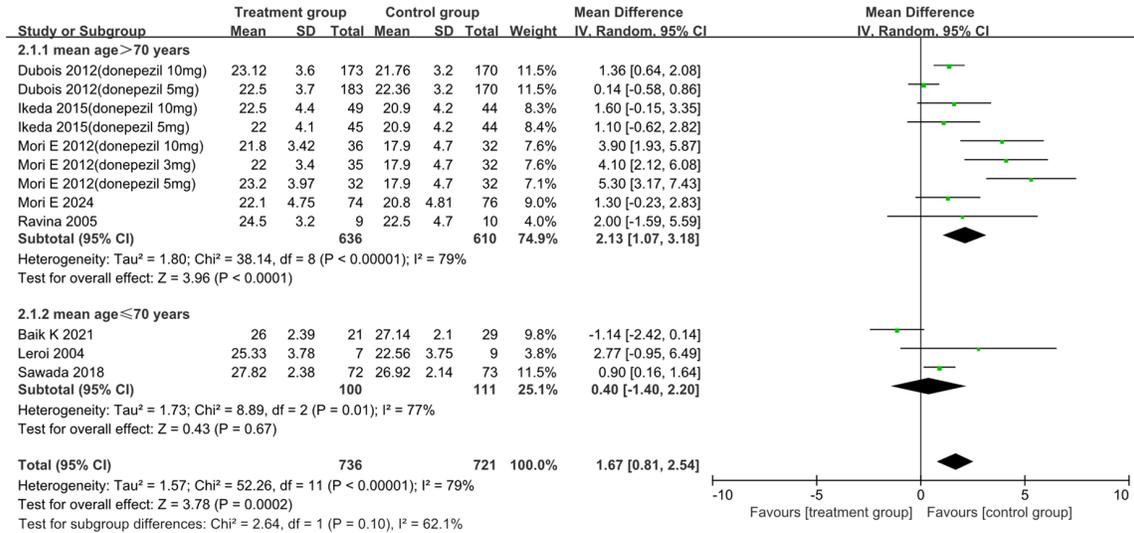


Figure 4. Subgroup analysis of MMSE scores based on average patient age.

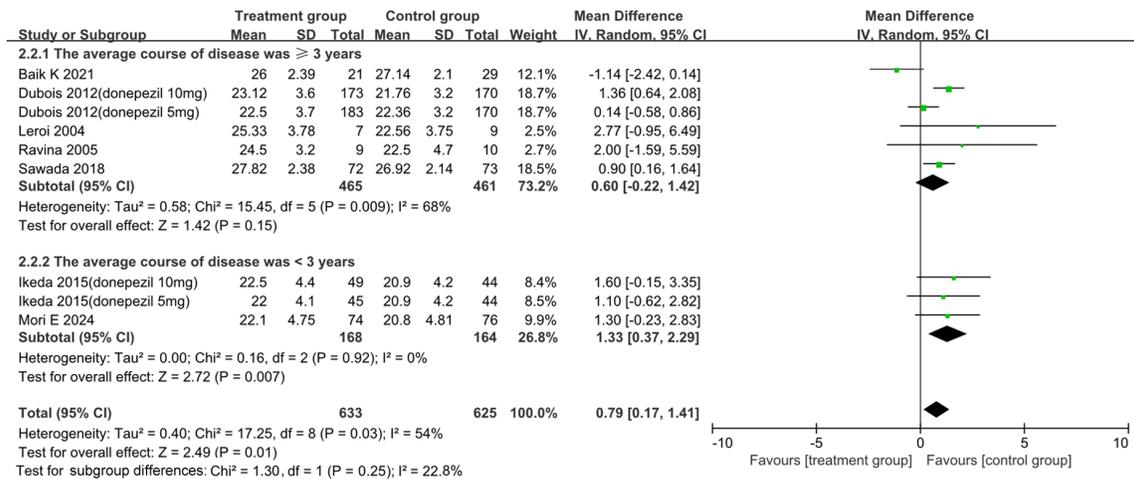


Figure 5. Subgroup analysis of mini-mental state examination scores for patients with average disease duration.

among the studies ($I^2 = 79\%$), and a random-effects model was used, yielding statistically significant results (SMD = 1.67, 95% CI [0.81, 2.54], $P < 0.0001$), indicating that the treatment group had higher MMSE scores than the control group.

For the subgroup with an average patient age > 70 years (5 studies), significant heterogeneity was found ($P < 0.00001$, $I^2 = 79\%$). A random-effects model revealed significant results (SMD = 2.13, 95% CI [1.07, 3.18], $P = 0.001$), showing that the treatment group had significantly higher MMSE scores. For the subgroup with an average age ≤ 70 years (3 studies), het-

erogeneity was present ($I^2 = 77\%$), and the random-effects model showed no significant difference between the treatment and control groups (SMD = 0.40, 95% CI [-1.40, 2.20], $P = 0.67$).

Subgroup analyses based on the mean disease duration (≥ 3 years or < 3 years) were also conducted. For the subgroup with a disease duration of ≥ 3 years (5 studies), heterogeneity was observed ($P = 0.009$, $I^2 = 68\%$). The random-effects model revealed no significant difference between the treatment and control groups (SMD = 0.60, 95% CI [-0.22, 1.42], $P = 0.15$) as shown in **Figure 5**.

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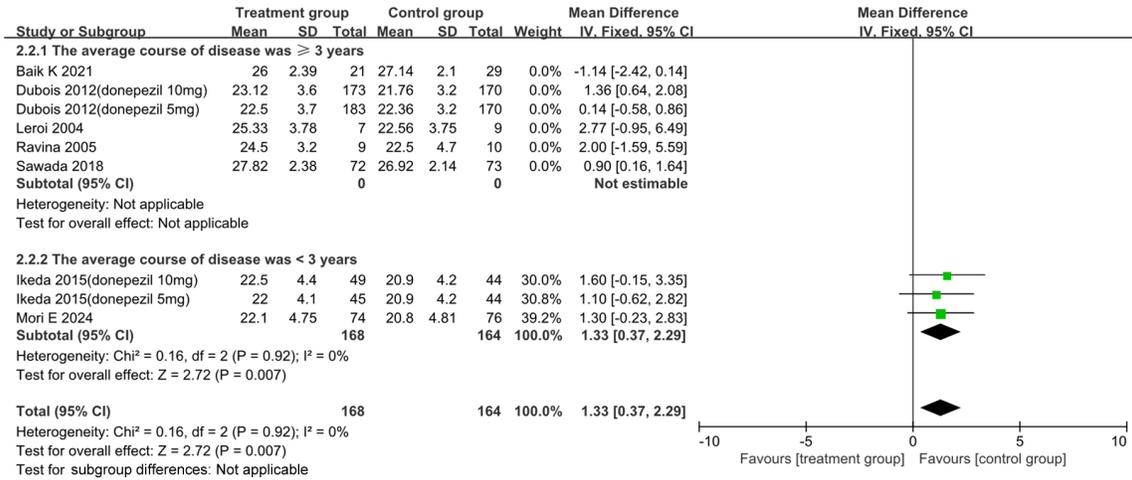


Figure 6. Subgroup analysis of mini-mental state examination scores for patients with average disease duration < 3 years.

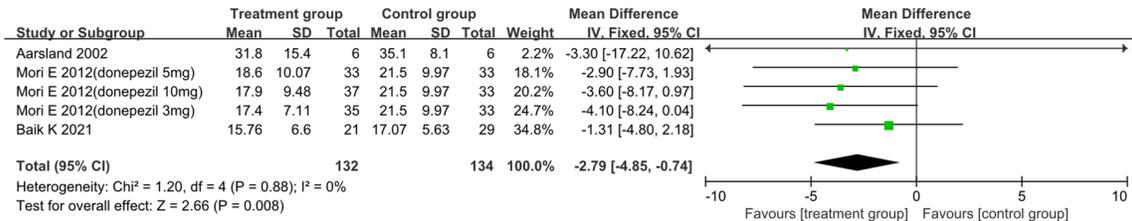


Figure 7. Forest Plot of Unified Parkinson's disease rating scale score comparison between the two groups.

For the subgroup with a disease duration of < 3 years (2 studies), no heterogeneity was found (P = 0.92, I² = 0%), and the fixed-effect model showed significant results, indicating that the treatment group had higher MMSE scores than the control group (SMD = 1.33, 95% CI [0.37, 2.29], P = 0.007), as shown in **Figure 6**.

UPDRS scores: Three studies assessed UPDRS scores, involving a total of 200 patients (68 in the control group and 132 in the treatment group). There was no significant heterogeneity across the studies (P = 0.88, I² = 0%), so a fixed-effect model was applied. The analysis revealed that the UPDRS scores in the treatment group were significantly lower than in the control group (SMD = -2.79, 95% CI: -4.85 to -0.74, P = 0.008), as shown in **Figure 7**.

CIBIC+ scores: Two studies used the CIBIC+ score, involving 529 patients (176 in the control group and 353 in the treatment group). There was no significant heterogeneity across the studies (P = 0.47, I² = 0%), so a fixed-effect

model was applied. The results showed that the CIBIC+ score in the treatment group was significantly lower than in the control group (SMD = -0.27, 95% CI: -0.45 to -0.08, P = 0.004), as shown in **Figure 8**.

ADAS-Cog scores: Two studies used the ADAS-Cog score to assess patients, involving a total of 526 participants-176 in the control group and 350 in the treatment group. The heterogeneity analysis revealed no significant differences across these studies (P = 0.93, I² = 0%), leading to the use of a fixed-effect model. The results showed a statistically significant difference in ADAS-Cog scores, with the treatment group outperforming the control group, as indicated by the diamond representing the pooled effect size not crossing the null effect line (SMD = -1.33, 95% CI: -2.68 to 0.03, P = 0.05) (see **Figure 9**).

NPI-2 scores: Three studies assessed outcomes using the NPI-2 score, involving a total of 300 participants. The analysis revealed no

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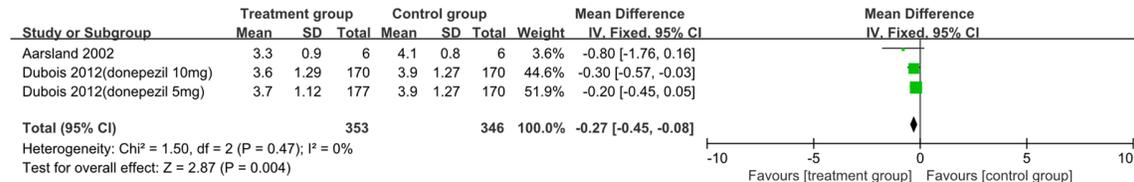


Figure 8. Meta-analysis of clinician's interview-based impression of change + scores between the two groups.

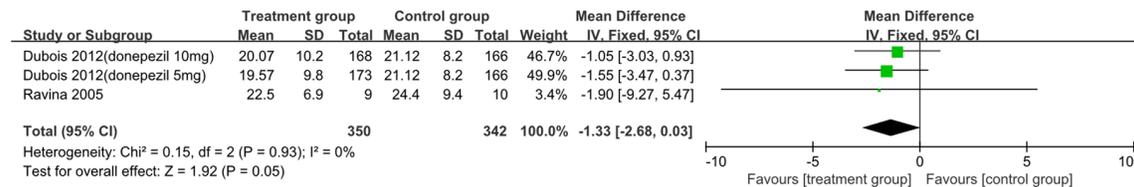


Figure 9. Meta-Analysis of Alzheimer's disease assessment scale-cognitive subscale scores between the two groups.

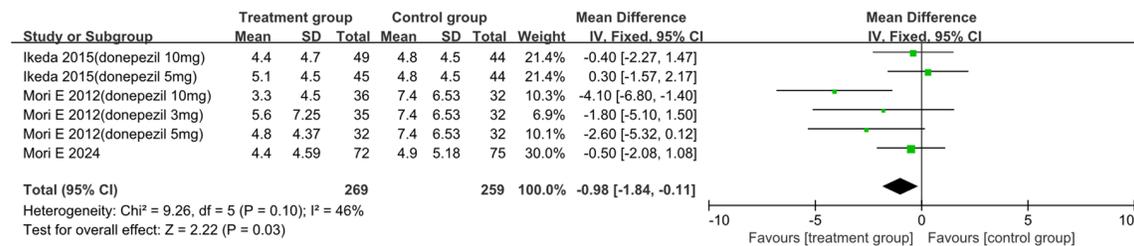


Figure 10. Meta-analysis of neuropsychiatric inventory -2 scores between the two groups.

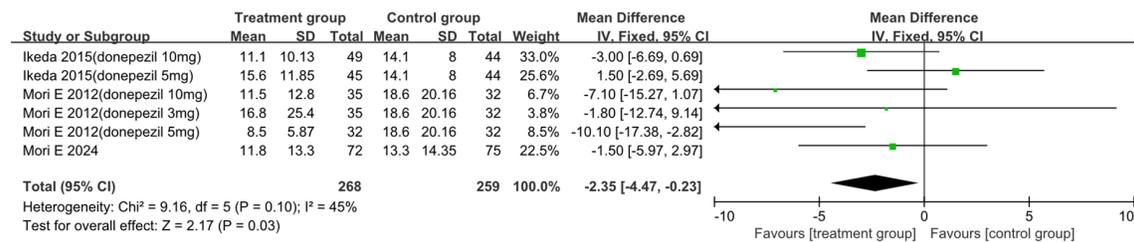


Figure 11. Meta-analysis of neuropsychiatric inventory -10 score comparison between the two groups.

significant heterogeneity across the studies (P = 0.10, I² = 46%), leading to the use of a fixed-effect model. The findings showed no statistically significant difference in NPI-2 scores between the treatment and control groups (SMD = -0.98, 95% CI: -1.84 to -0.11, P = 0.03), as shown in **Figure 10**.

NPI-10 scores: Three studies evaluated outcomes using NPI-10 scores, with a total of 300 patients. No considerable heterogeneity was observed across the studies (P = 0.10, I² = 45%), so a fixed-effect model was applied. The results indicated a statistically significant dif-

ference in NPI-10 scores between the treatment and control groups (SMD = -2.53, 95% CI: -4.47 to -0.23, P = 0.03), as shown in **Figure 11**.

Adverse reactions

Nine studies reported adverse reactions. No heterogeneity was detected among the studies (P = 0.80, I² = 0%), so a fixed-effect model was adopted, as shown in **Figure 12**. The findings revealed that the overall occurrence rate of adverse reactions across all patients was 40.54% (581/1433). Specifically, the occur-

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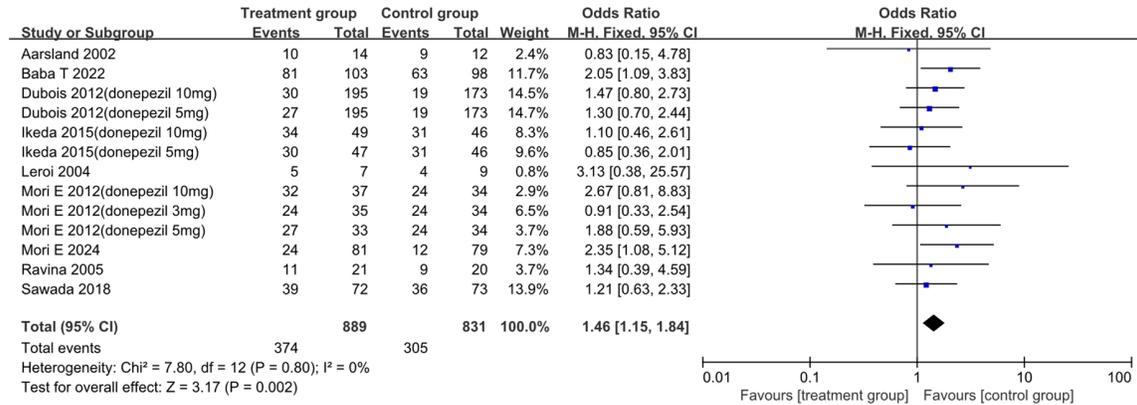


Figure 12. Meta-analysis of adverse reactions between the two groups. Publication bias.

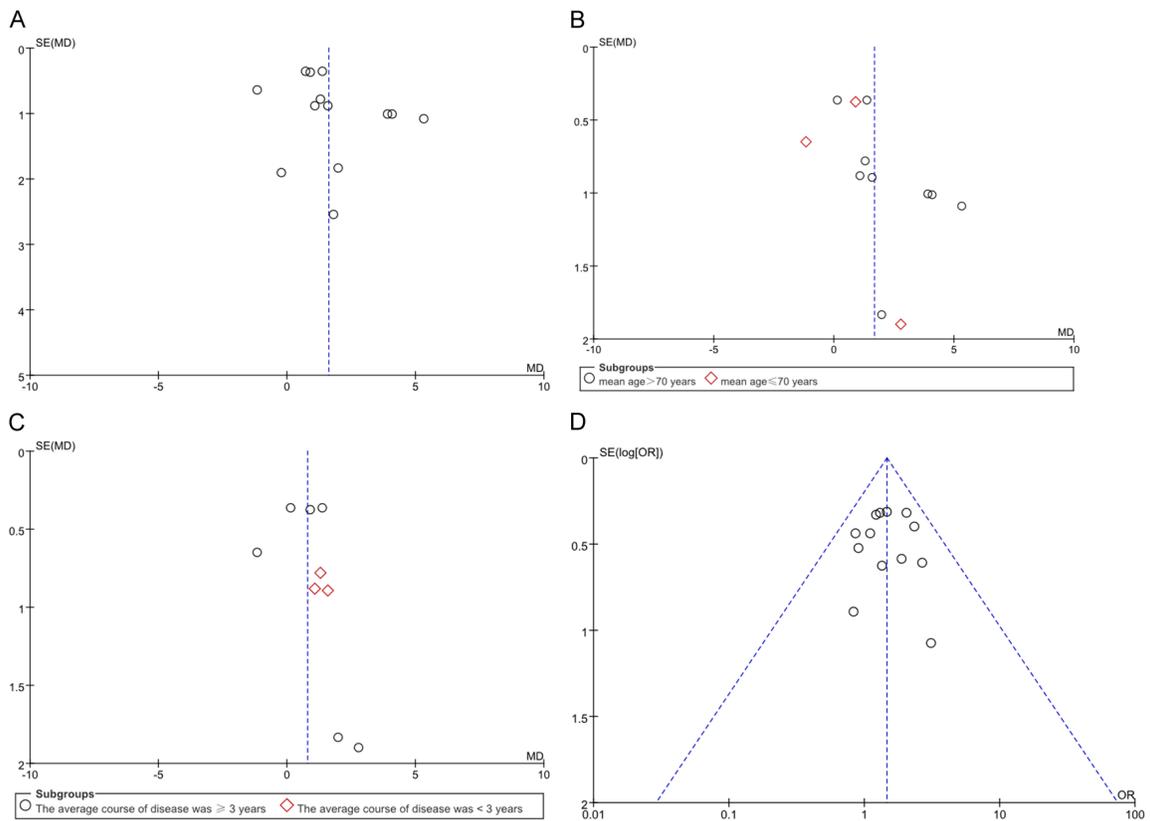


Figure 13. Funnel Plots. Note: (A) Funnel plot based on MMSE score analysis results; (B) Funnel plot of the impact of average age subgroups on MMSE scores; (C) Funnel plot of the impact of average disease duration subgroups on MMSE scores; (D) Funnel plot based on adverse reaction analysis results. Mini-Mental State Examination (MMSE).

rence rate in the treatment group was 42.07% (374/889), while in the control group, it was 38.05% (207/544). The occurrence of adverse reactions was significantly higher in the treatment group compared to the control group (RR = 1.46, 95% CI [1.15, 1.84], P = 0.002).

Reporting bias assessment

The funnel plots for MMSE scores and adverse reactions of the included studies are shown in **Figure 13**. The asymmetry of the funnel plots suggests potential bias in the studies. While

most studies fall within the 95% confidence interval, the left and right distributions are notably asymmetric, indicating a possible publication bias.

Discussion

As the global population ages, the incidence of PD continues to rise annually. PD is characterized by a variety of symptoms, including resting tremor, bradykinesia, stiffness, postural instability, and cognitive impairment, all of which severely affect patients' ability to live independently [21, 22]. Cognitive impairment is a common non-motor symptom of PD, encompassing both mild cognitive impairment and PD dementia. Studies show that mild cognitive impairment affects approximately 25% of PD patients [23], and it may even precede motor symptoms early in the disease course. Pharmacotherapy remains the primary treatment for PD. However, as non-motor symptoms emerge and the disease progresses, both motor and non-motor symptoms typically worsen [24]. The efficacy of commonly used medications declines with long-term use, and the incidence of adverse reactions increases.

The etiology of PD is still not fully understood, but it is primarily caused by the degeneration and death of dopaminergic neurons in the substantia nigra, leading to reduced dopamine levels and an imbalance between dopamine and acetylcholine neurotransmitters in the brain [25, 26]. Donepezil hydrochloride, a commonly used cholinesterase inhibitor, has been shown to inhibit acetylcholinesterase hydrolysis and protect cholinergic neurons in the central nervous system. Clinical evidence suggests that cognitive impairment in PD is associated with cholinergic dysfunction [27, 28]. By promoting neuroplasticity, donepezil helps improve learning and cognitive functions, leading to significant cognitive recovery. Therefore, donepezil can be considered a first-line treatment for PD.

In the present study, a meta-analysis was conducted to assess the therapeutic efficacy of donepezil in PD by analyzing RCTs focused on donepezil for PD treatment. The primary outcomes were MMSE scores and the incidence of adverse reactions, while secondary outcomes included CIBIC+ scores, ADAS-Cog scores, and NPI-2 scores. The MMSE, a widely recognized tool, is used globally to assess cognitive func-

tion in diseases such as Alzheimer's and PD. The analysis revealed that after donepezil treatment, the MMSE scores in the treatment group were significantly higher than those in the control group. These results suggest that donepezil significantly improves cognitive decline in PD patients, consistent with previous studies [29, 30]. However, considerable heterogeneity was observed across the included studies. Subgroup analyses based on the average age and disease duration of patients showed that disease duration may contribute to heterogeneity. The subgroup analysis also indicated higher MMSE scores in the treatment group. Pagano et al. [31] found that cholinesterase inhibitors, including donepezil, could significantly slow the decline in MMSE scores and improve behavioral disturbances, but motor function improvements were not observed. This contrasts with our study, which showed a reduction in UPDRS scores. We speculate that the treatment duration may explain this discrepancy, as the trials in our study typically lasted 12 weeks or more, while Pagano's study had a shorter treatment period (10-26 weeks) [31]. This suggests that long-term donepezil treatment may better regulate motor function, possibly by indirectly improving the dopamine-acetylcholine neurotransmitter balance following increased acetylcholine levels [28].

Donepezil hydrochloride can cause various adverse reactions, such as sleep disorders, withdrawal syndrome, mania, myoclonus, hepatic and cardiac adverse reactions, and rashes [32-38]. This study also analyzed the adverse reactions associated with donepezil in PD treatment. No heterogeneity was found in the studies, with the overall adverse reaction rate being 40.54%. The treatment group had a significantly higher adverse-event rate compared to the placebo group. These findings suggest that when using donepezil to treat PD, clinicians should be cautious of gastrointestinal issues (e.g., nausea and vomiting) and other adverse reactions, including dizziness, headache, sleep disorders, and tremors.

Due to limitations in study types, subjects, and data extraction, the number of eligible studies included in this meta-analysis was limited, potentially introducing selection bias. Some factors were only addressed in a few

studies, which may have influenced the results. Additionally, significant differences in sample sizes among the studies may have affected the accuracy of the results. Therefore, further high-quality, large-scale studies are needed to provide more robust evidence.

In summary, the results of this meta-analysis indicate that donepezil treatment significantly improves MMSE scores and cognitive decline in PD patients compared to placebo or conventional therapy. However, the incidence of adverse reactions is higher with donepezil treatment, suggesting that clinicians must carefully weigh the cognitive benefits against the risks of adverse reactions when using donepezil in clinical practice.

Disclosure of conflict of interest

None.

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