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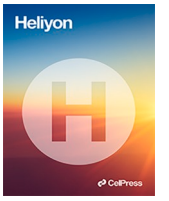

Review article

Dose–response relationship of levodopa with dyskinesia in Parkinson's disease: A systematic review and meta-analysis

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ABSTRACT

Despite existing evidence linking dyskinesia to levodopa, the primary treatment for Parkinson's, the dose–response relationship and risk factors remain uncertain. In this study, the risk for dyskinesia in patients with Parkinson's disease receiving levodopa was evaluated via meta-analysis and meta-regression approaches to examine dyskinesia risk factors more reliably and improve treatment strategies and patient care. The PubMed and Embase databases were searched to identify randomized controlled trials comparing levodopa with other anti-Parkinson's drugs published in English before June 31, 2023. The primary outcome was dyskinesia, and a risk of bias assessment was performed. In total, 24 studies met the inclusion criteria; 21 had a low risk of bias, and 3 had a high risk of bias. These studies included 4698 patients with Hoehn and Yahr Grade I–III Parkinson's disease. Our meta-analysis showed that the risk of dyskinesia was higher for levodopa than for other anti-Parkinson's drugs (odds ratio: 2.52 [95% confidence interval: 1.84–3.46]). Dyskinesia was not related to age (slope coefficient: 0.185 [0.095]; $P = 0.061$), disease duration (slope coefficient: 0.011 [0.018]; $P = 0.566$), or treatment duration (slope coefficient: 0.008 [0.007]; $P = 0.216$). The mean levodopa equivalent dose (slope coefficient: 0.004 [0.001]; $P = 0.001$) in the experimental group and the differences in drug doses between the experimental and control groups were correlated with the risk of dyskinesia. Results of randomized controlled trials supported an association between the levodopa dose and dyskinesia in patients with Parkinson's disease. Compared with levodopa users, users of other anti-Parkinson's drugs had a lower incidence of dyskinesia. Age, disease duration, and treatment duration were not correlated with dyskinesia. These findings suggest that anti-Parkinson's drugs other than levodopa, particularly in cases of early-stage Parkinson's disease, should be considered to reduce the risk of dyskinesia.

1. Introduction

Dyskinesia, a severe side effect commonly observed in patients undergoing long-term treatment for Parkinson's disease, is

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characterized by involuntary, erratic, writhing movements of the face, arms, legs, or trunk. This distressing condition not only significantly impacts the quality of life of patients but also substantially burdens their families and society. Although there is existing epidemiological evidence hinting at a connection between dyskinesia and levodopa [1], the primary treatment for Parkinson's disease and the precise nature of the dose–response relationship, between dyskinesia remains unclear. Some previous meta-analyses have explored the correlation between levodopa dosage and dyskinesia; however, the knowledge about the risk factors associated with dyskinesia in Parkinson's disease remains limited [2–4]. The shortcomings of relying solely on single randomized controlled trials (RCTs) to draw conclusions regarding risk factors for dyskinesia are evident because of potential issues related to study design, methodology, and the evaluation of movement disorders. To overcome these limitations and obtain more reliable insights, we conducted an extensive systematic review and meta-analysis in this study, incorporating a meta-regression analysis. By pooling data from multiple RCTs, this approach aims to provide a more robust and comprehensive examination of risk factors contributing to dyskinesia in Parkinson's disease. This study aimed to obtain a clearer understanding of the underlying factors associated with the development of dyskinesia, ultimately leading to improved treatment strategies and enhanced patient care.

2. Results

2.1. Study selection

A total of 2351 studies were identified, of which 245 duplicates were removed. Subsequently, after screening the titles and abstracts, another 2015 studies were excluded. After reading the full text of the remaining 91 studies, another 67 studies were excluded. A total of 24 studies [5–28] met the inclusion criteria and were included in the meta-analysis (Fig. 1).

2.2. Characteristics of the included studies

In total, 2349 and 4698 patients were included in the experimental and control groups, respectively. The mean sample size was 180 (range: 28–587). Most patients had Hoehn and Yahr Grade I–III Parkinson's disease. Dyskinesia was the primary outcome in 17 studies [8–12,14–18,21–28]. Studies with multiple courses were included because we considered the treatment course a risk factor. In total, 10 studies summarized the results of four RCTs of multiple courses [9–11,14,15,21,23,25–27]. Of the 24 studies finally included, in one trial, two drugs were compared with levodopa [21], and in two trials, levodopa was compared with a placebo [7,19]. A total of 21 trials had a low risk of bias [5–23,26,28], and three trials had a high risk of bias [24,25,27].

The median age of patients was 62.3 years (interquartile range [IQR]: 61.2–63.7 years). The median disease duration at the start of

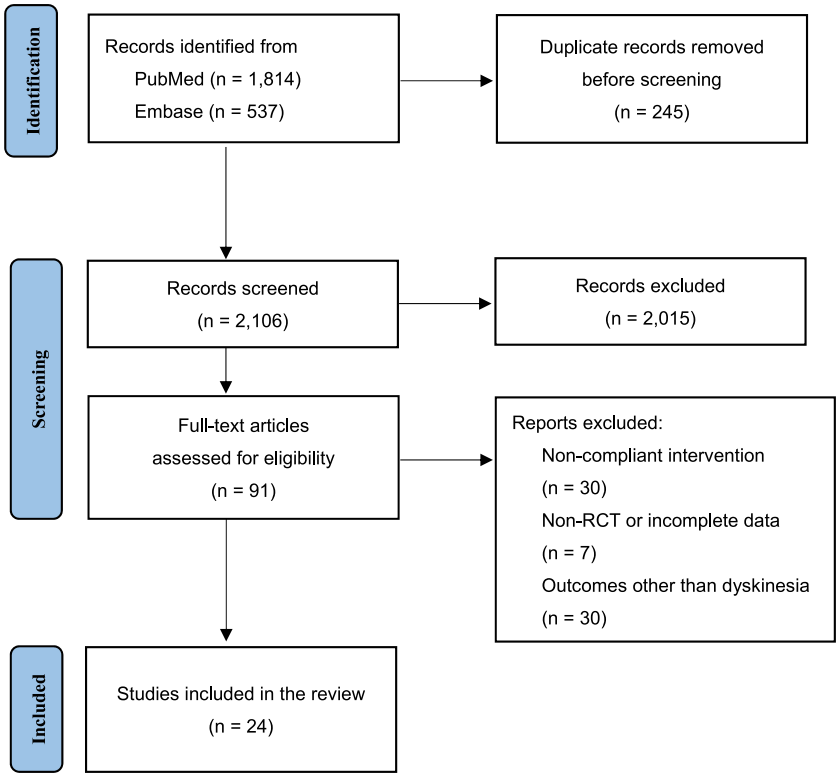

Fig. 1. Flow chart of included studies.

Table 1
Characteristics of included studies.

Ref.	Participants (n)	Mean age (years)	Mean disease duration (months)	Treatment duration (months)	Drugs (exp. group)	Mean LED (exp. group; mg)	Mean LD dose (exp. group; mg)	Mean LD dose (ctrl group; mg)	Patients administered LD (exp. group; n)	Patients with dyskinesia administered LD (exp. group; n)	Patients with dyskinesia (exp. group; total; n)	Patients (ctrl group; total; n)	Patients with dyskinesia (ctrl group; n)
[13]	520	63.2	14.0	48	Selegiline	10 (100)	460.0	635.0	271	98	98	249	79
[14]	520	63.2	14.0	36	Selegiline	10 (100)	352.0	420.0	271	92	92	249	67
	511	62.4			Bromocriptine	36 (360)	0.0		0	0	5		
[15]	154	64.3	48.6	60	Selegiline	10 (100)	424.0	506.0	73	27	27	81	25
[16]	50	60.3	8.3	44	Bromocriptine	24.2 (242)	515.4	725.6	27	4	4	23	11
[17]	587	63.7	20.5	48	Bromocriptine	13.8 (138)	308.0	439.0	285	42	42	302	62
[18]	412	61.5	23.4	45	Cabergoline	3 (200)	303.0	637.0	135	8	12	204	28
[19]	82	59.0	20.7	60	Lisuride	1.03 (103)	387.5	446.7	41	8	8	41	14
[20]	268	63.0	29.7	60	Ropinirole	16.5 (330)	427.0	753.0	92	27	36	89	40
[21]	182	64.6	5.5	42	Placebo	0	0.0	150.0	0	0	3	92	3
	178	64.4	6.4					300.0				88	2
	181	65.1	5.7					600.0				91	15
[22]	419	61.4	22.8	60	Cabergoline	2.9 (193.3)	431.0	784.0	135	19	20	208	44
[23]	222	60.2	19.8	72	Pramipexole	3.2 (320)	385.9	404.5	98	ND	22	114	42
[24]	91	62.3	22.2	60	Cabergoline	2.9 (193.3)	325.0	336.0	20	0	0	46	3
[25]	294	58.9	<24	36	Pergolide	3.23 (323)	0.0	504.0	0	0	12	146	38
[26]	301	61.2	19.8	48	Pramipexole	2.78 (278)	434.0	702.0	109	27	37	150	81
[27]	301	61.2	19.8	23.5	Pramipexole	2.78 (278)	264.0	509.0	80	10	15	150	46
[28]	60	61.5	32.4	72	Bromocriptine	80 (800)	471.0	569.0	27	3	3	29	14
[29]	28	60.9	27.3	36	Bromocriptine	50 (500)	0.0	444.2	0	0	0	13	3
[30]	179	64.6	24.5	7.5	Placebo	0	0.0	435.0	0	0	0	87	2
	196	65.3	21.6					735.0				104	4
	190	65.1	22.8					1170.0				98	5
[31]	140	63.4	35.4	78	Selegiline	10 (100)	590.0	710.0	71	25	25	69	27
[32]	162	60.5	15.9	24	Ropinirole	12.2 (244)	ND	558.7	15	1	3	75	20
[33]	126	62.0	23.5	60	Bromocriptine	28 (280)	590.6	494.0	30	17	17	64	35
[34]	126	62.0	23.5	36	Bromocriptine	29.5 (295)	445.7	437.9	33	5	5	64	7
[35]	69	62.1	25.9	120	Ropinirole	14.5 (290)	631.7	800.2	39	ND	22	27	21
[36]	511	62.4	14.0	120	Bromocriptine	36 (360)	516.0	663.0	254	117	117	249	134

Abbreviations: Ctrl, control; Exp., experimental; LD, levodopa; LED, levodopa equivalent dose; ND, no data; No., number; Ref., reference.

the trial was 21.2 months (IQR: 14.0–23.8 months). The median levodopa dose was significantly lower in the experimental group than in the control group (368.95 mg [IQR: 0.00–449.28 mg] vs. 509.00 mg [IQR: 437.90–702.00 mg], respectively). The median LED (levodopa equivalent dose) in the experimental group was 200.00 mg (IQR: 100.00–295.00 mg). The detailed characteristics of the included studies are shown in Table 1.

2.3. Comparison of the association between dyskinesia risk and levodopa or other Anti-Parkinson's drugs

Fig. 2 shows that levodopa was associated with a higher risk of dyskinesia than other anti-Parkinson's drugs (OR: 2.52 [95% confidence interval (CI): 1.84–3.46]). We observed a high heterogeneity among studies ($I^2 = 78.7\%$; $P < 0.001$). This heterogeneity was likely due to the inclusion of studies involving drugs other than levodopa for Parkinson's disease. Additionally, the effects of these drugs on motor disorders may vary, resulting in significant clinical heterogeneity. The Begg and Mazumdar rank correlation test (after correcting for continuity) showed no significant publication bias ($P = 0.631$).

2.4. Risk factors for dyskinesia

2.4.1. Age, disease duration, and treatment duration

Age, disease duration, and treatment duration were reported in all 24 studies. One trial with a disease duration of <24 months was excluded because the treatment duration could not be determined [18]. Meta-regression showed that age (SE: 0.185 [0.095]; $P = 0.061$), disease duration (SE: 0.011 [0.018]; $P = 0.566$), and treatment duration (SE: 0.011 [0.018]; $P = 0.566$) were not associated with the risk of dyskinesia.

2.4.2. Drug dose

The mean levodopa dose in the control group was reported in all 24 studies, while that in the experimental group was reported in 17 studies [5,6,8,10–15,17,20–22,24–27]. Seven studies were excluded from the meta-analysis: four studies did not involve levodopa administration during the trial [7,16,18,19], one study did not report the levodopa dose [28], and two studies did not state the number of patients treated with levodopa or the number of patients with dyskinesia [9,23]. The mean dose of anti-Parkinson's drugs (converted to LED) in the experimental group was reported in 22 studies [5,6,8–18,20–28]. The experimental group was administered a placebo in the other two studies, which were excluded from the meta-analysis [7,19].

Meta-regression showed that the mean levodopa dose in the control (SE: 0.001 [0.001]; $P = 0.319$) and experimental (SE: 0.001

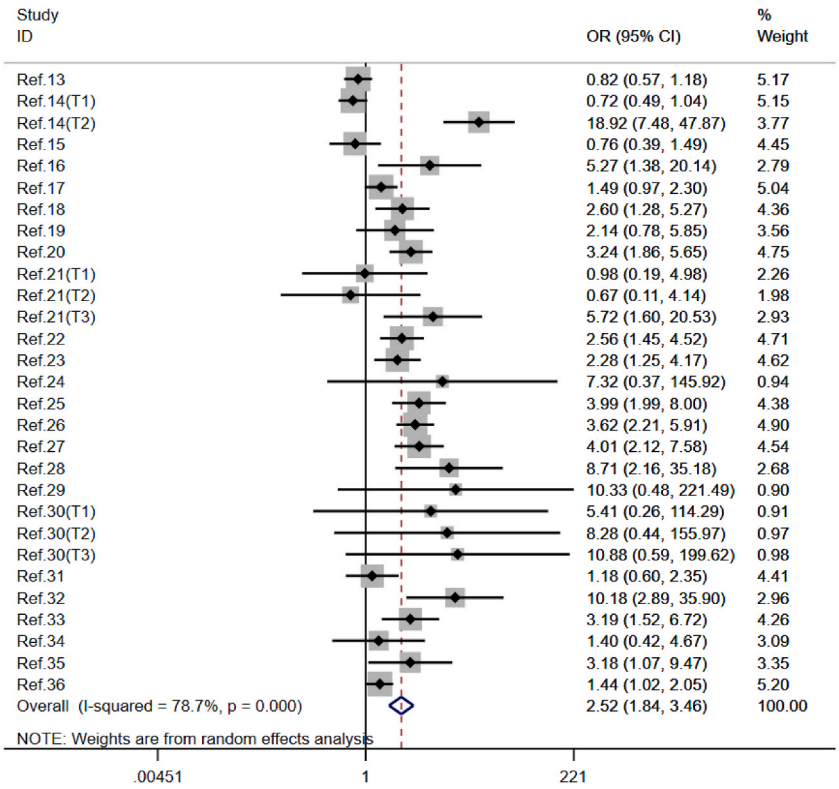

Fig. 2. Difference between the effects of levodopa and other anti-Parkinson's drugs on dyskinesia. Overall: pooled odds ratio (OR) for all studies, CI: confidence interval.

[0.002]; $P = 0.481$) groups was not associated with the risk of dyskinesia. In contrast, the mean LED in the experimental group (SE: 0.004 [0.001]; $P = 0.001$) was negatively associated with the risk of dyskinesia (Fig. 3).

2.4.3. Dose differences

Dose differences included differences in the levodopa dose between the control and experimental groups and between the levodopa dose in the control group and the LED in the experimental group. Meta-regression showed that differences in the mean levodopa dose (SE: 0.003 [0.001]; $P = 0.037$) and ratio (SE: 1.020 [0.417]; $P = 0.027$) between the control and experimental groups were negatively associated with the risk of dyskinesia (Fig. 4). The difference between the mean levodopa dose in the control group and the mean LED in the experimental group (SE: 0.001 [0.001]; $P = 0.298$) was not associated with the risk of dyskinesia. In contrast, the ratio (SE: 0.315 [0.079]; $P = 0.001$) was positively associated with the risk of dyskinesia (Fig. 5). These results indicate that the difference in the mean levodopa dose and the ratio between the control and experimental groups were negatively associated with the risk of dyskinesia. Further, these results also show that the ratio between the mean levodopa dose in the control group and the mean LED in the experimental group was positively associated with the risk of dyskinesia.

3. Materials and methods

3.1. Data sources and search strategy

A systematic literature search of the PubMed and Embase databases was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [29]. Details of the protocol for this systematic review and meta-analysis were registered on OSF and can be accessed at https://osf.io/b2e8c/. The following keywords were used to identify relevant studies published in English before June 31, 2023: "Parkinson" AND "levodopa" AND ("early" OR "*de novo*" OR "untreated").

3.2. Inclusion and exclusion criteria

The inclusion criteria were as follows. (1) Participants: patients diagnosed with early-stage Parkinson's disease without movement disorders who were untreated or treated for <12 months. (2) Interventions: a control group administered levodopa, and an experimental group administered other anti-Parkinson's drugs with or without levodopa. In cases where levodopa is administered at or after the trial's commencement, the mean levodopa dose in the experimental group should be less than that in the control group to prevent symptoms from worsening. The number/percentage of patients who develop dyskinesia before levodopa administration should be included. (3) Outcome: the number of patients with dyskinesia. (4) Study design: RCT.

Studies of patients with severe complications, reviews, epidemiological and animal studies, as well as duplicate publications were excluded.

3.3. Study selection

After duplicates from PubMed and Embase were removed, three reviewers (T.H., D.W., and X.y.Z.) independently confirmed that the inclusion criteria were met. Titles and abstracts were screened, and studies not meeting the inclusion criteria were excluded. The full text of the remaining articles was independently assessed for eligibility. Disagreements were resolved through discussion.

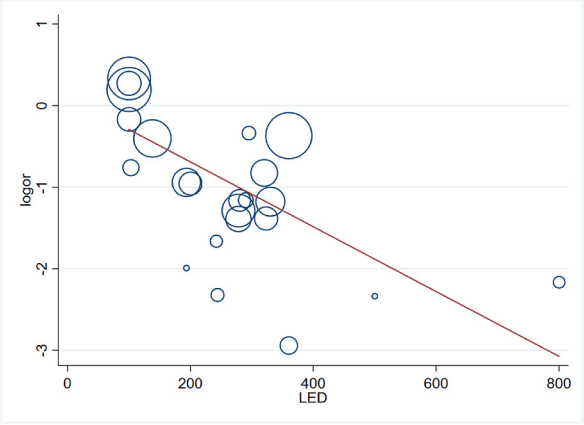

Fig. 3. Meta-regression linear prediction plot of the relationship between the average dose of LED and dyskinesia.

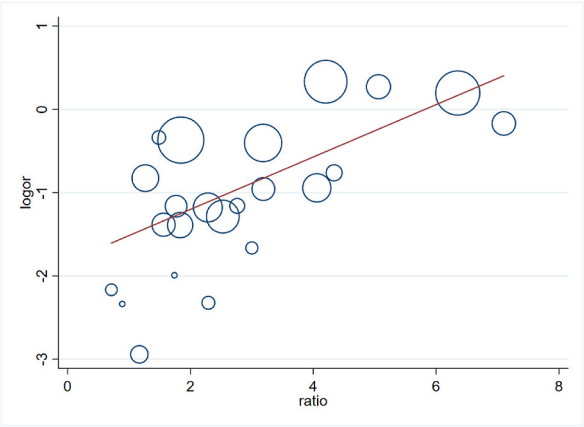

Fig. 4. Meta-regression linear prediction plot of the relationship between LD/LED and dyskinesia.

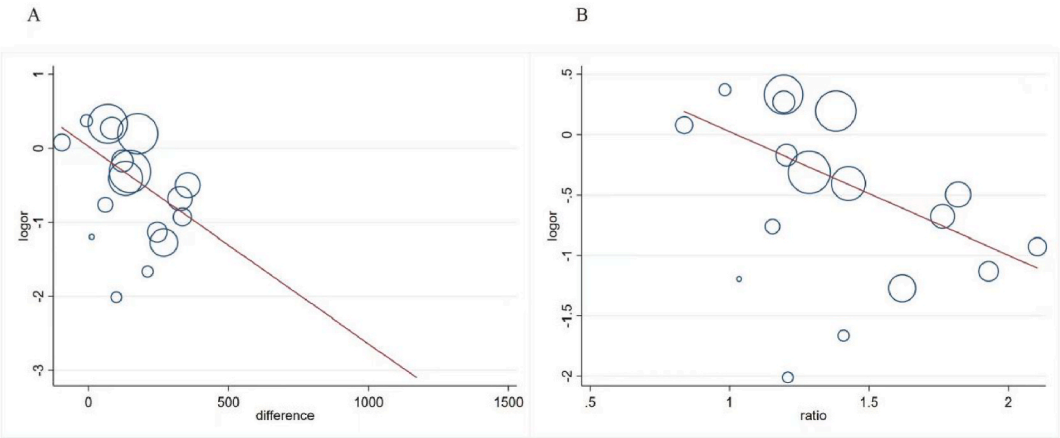

Fig. 5. Meta-regression linear prediction plot of the relationship between the ratio and difference in drug dose and dyskinesia. a: Relationship between the difference in drug dose and dyskinesia; b: Relationship between the ratio of drug dose and dyskinesia. The term "ratio" refers to the ratio of the mean levodopa dose in the control group to the mean levodopa equivalent dose (LED) in the experimental group. Each bubble represents an individual study. The size is proportional to the inverse of the variance of the dyskinesia estimate for that study.

3.4. Data extraction

The following data were extracted by one author (T.H.) and independently checked by a second author (D.W.): author, year of publication, whether dyskinesia was the primary outcome, sample size, age, disease duration, treatment duration, Hoehn and Yahr classification, and drug names and doses. A third author (X.y.Z.) independently checked the following: authors, number of patients with Parkinson's disease, number of patients with dyskinesia, number of patients treated with levodopa in the experimental group, and number of patients with dyskinesia in the experimental and control groups. Dose differences between the experimental and control groups were examined to determine whether drug dose is a risk factor for dyskinesia. The dose difference was defined as the difference between the drug dose in the experimental group and the levodopa dose in the control group. The drug dose in the experimental group was the dose of levodopa or other anti-Parkinson's drugs. Dose differences are expressed as mean values and ratios. The drug dose was set to zero when a placebo was administered instead of levodopa. Studies with insufficient and missing data were excluded from the meta-analysis.

3.5. Risk of bias

Three reviewers (T.H., D.W., and X.y.Z.) independently assessed the risk of bias using the Cochrane Collaboration's Risk of Bias Tool) [30]. Each reviewer scored each item as "high," "low," or "unclear" risk of bias. Disagreements were resolved through discussion.

3.6. Statistical analysis

A meta-analysis of the included studies was performed to calculate odds ratios (ORs) and 95% CIs. The contribution (weight) of each study to the overall estimate is presented in forest plots. Summary estimates and 95% CIs were calculated using Mantel–Haenszel-weighted random-effects models [31]. Heterogeneity was assessed using the I^2 statistic [32]. Because the number of studies included in this meta-analysis was >10 and the data were dichotomous, the Begg and Mazumdar rank correlation test [33] was used to assess publication bias.

The regression model proposed by Orsini et al. [34], based on the generalized least-squares method, requires data extracted from case-control or cohort studies. However, no study on dyskinesia met these criteria. Therefore, meta-regression was used to evaluate correlations between the drug dose and other potential risk factors and dyskinesia. The LED [35] was used to determine whether non-levodopa drugs are risk factors for dyskinesia. Age, disease duration, treatment duration, dose, and dose differences were used as covariables in the meta-regression. Slope coefficients (SEs) and corresponding *P*-values were computed via linear regression [36]. Statistical analyses were performed using Stata (version 15.0; Stata Corp., College Station, TX, USA). $P < 0.05$ was considered statistically significant.

4. Discussion

We conducted a systematic review and meta-analysis to provide a more reliable and comprehensive examination of dyskinesia risk factors, enhancing treatment strategies and patient care. We found that the risk of dyskinesia was significantly higher for levodopa than for other anti-Parkinson's drugs or placebo and increased in a dose-dependent manner. However, the high clinical heterogeneity limited the interpretation of our findings, and the meta-regression failed to demonstrate an association between levodopa dose and the risk of dyskinesia. Nonetheless, the difference in the mean levodopa dose between the control and experimental groups was negatively associated with the risk of dyskinesia. This can be explained either by an increase in the levodopa dose in the control group or a decrease in the levodopa dose in the experimental group, both of which negatively affect dyskinesia. When the significance threshold was set at $P < 0.01$, differences in the levodopa dose between the control and experimental groups were not associated with the risk of dyskinesia. Moreover, linear regression analysis revealed no correlation. In contrast, at $P < 0.01$, the LED in the experimental group as well as the ratio between the levodopa dose in the control group and the LED in the experimental group were associated with dyskinesia risk. Significant correlations were found through a linear regression analysis ($P = 0.001$). LED in the experimental group was negatively associated with the risk of dyskinesia, suggesting that the use of other anti-Parkinson's drugs is related to a lower risk of dyskinesia. Thus, other anti-Parkinson's drugs may have a protective effect against dyskinesia, contrary to the results of previous studies [37,38]. This protective effect may be related to the reduced levodopa dose, as the increased use of other anti-Parkinson's drugs corresponds with the decreased use of levodopa. However, this notion requires further investigation. The ratio between the levodopa dose in the control group and the LED in the experimental group was positively associated with the risk of dyskinesia, suggesting that the lower the LED, the greater the risk of dyskinesia, consistent with the effect of LED on dyskinesia. An increase in levodopa dose was associated with a higher risk of dyskinesia, consistent with clinical experience and previous findings [3,37,39]. Age, disease duration, and treatment duration were not associated with the risk of dyskinesia. These factors cannot be considered sources of heterogeneity in this study.

There were considerable differences in the experimental design among the included studies. A placebo was administered to the experimental group in two studies and compared with different doses of levodopa [7,19], whereas the levodopa dose was fixed in the other 22 studies [5,6,8–18,20–28]. In some studies, the control group included combinations of levodopa and other anti-Parkinson's drugs, similar to that in the experimental group, which may result in bias because there is no consensus on the effects of other anti-Parkinson's drugs on dyskinesia. The experimental groups included placebo and seven non-levodopa, anti-Parkinson's drugs. Personalized treatments and lifestyle differences should also be considered, as these may lead to an ecological fallacy.

We considered the treatment course a risk factor and included RCTs with multiple courses. This may have led to the inclusion of some patients with movement disorders twice, increasing the probability of type I errors. The included studies varied considerably in the duration of follow-up (range: 7.5–120.0 months), contributing to the variation in experimental design. Meta-regression has low power for assessment of the dose–response relationship. It can only be applied to linear relationships, whereas most dose–response relationships are non-linear. The relationship between the levodopa dose and the risk of dyskinesia is probably non-linear. A dose–response meta-analysis based on the generalized least-squares method can be used to analyze linear and non-linear relationships [34]. However, it can only be used for case-control studies, person-years, or cumulative incidence in cohort studies and not for RCTs [40]. More advanced experimental designs are thus needed, and prospective studies on the association of drugs with dyskinesia should be conducted.

Despite these limitations, our results show that non-levodopa anti-Parkinson's drugs exert a protective effect against dyskinesia. These findings may contribute to the optimization of treatment strategies for Parkinson's disease, suggesting that other anti-Parkinson's drugs should be prioritized for patients with early-stage Parkinson's disease. The use of levodopa should be delayed to reduce the risk of dyskinesia, improve quality of life, and increase compliance. Further research is warranted to understand the underlying mechanisms.

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Natural Science Foundation of China.

Data statement

Data and analytic scripts are available at the Open Science Framework at https://osf.io/b2e8c/.

Ethics statement

Review and/or approval by an ethics committee was not needed for this study because it only included analyses of secondary and publicly available data. Informed consent was not required for this study because it only included analyses of secondary and publicly available data.

CRediT authorship contribution statement

Taozhi He: Data curation. **Dai Wang:** Writing – original draft. **Xinyu Zhang:** Writing – review & editing. **Jiawen Liu:** Formal analysis. **Shiyu Fang:** Data curation. **Zhe Zhang:** Supervision. **Hongjie Liu:** Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Hongjie Liu reports financial support was provided by National Natural Science Foundation of China (No. 82074306).

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