Original Paper

Comparison of the Efficacy of Different Drugs on Non-Motor Symptoms of Parkinson's Disease: a Network Meta-Analysis

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Key Words

Parkinson's disease • Non-motor symptoms • UPDRS • Apomorphine • Efficacy • Drug therapy • Randomized controlled trials • Bayesian network model

Abstract

Background/Aims: A network meta-analysis is used to compare the efficacy of ropinirole, rasagiline, rotigotine, entacapone, apomorphine, pramipexole, sumanirole, bromocriptine, piribedil and levodopa, with placebo as a control, for non-motor symptoms in Parkinson's disease (PD). **Methods:** PubMed, Embase and the Cochrane Library were searched from their establishment dates up to January 2017 for randomized controlled trials (RCTs) investigating the efficacy of the above ten drugs on the non-motor symptoms of PD. A network meta-analysis combined the evidence from direct comparisons and indirect comparisons and evaluated the pooled weighted mean difference (WMD) values and surfaces under the cumulative ranking curves (SUCRA). The network meta-analysis included 21 RCTs. **Results:** The analysis results indicated that, using the United Parkinson's Disease Rating Scale (UPDRS) III, the efficacies of placebo, ropinirole, rasagiline, rotigotine, entacapone, pramipexole, sumanirole and levodopa in treating PD were lower than that of apomorphine (WMD = -10.90, 95% CI = -16.12~-5.48; WMD = -11.85, 95% CI = -17.31~-6.16; WMD = -11.15, 95% CI = -16.64~-5.04; WMD = -11.70, 95% CI = -16.98~-5.60; WMD = -11.04, 95% CI = -16.97~-5.34; WMD = -13.27, 95% CI = -19.22~-7.40; WMD = -10.25, 95% CI = -15.66~-4.32; and WMD = -11.60, 95% CI = -17.89~-5.57, respectively). Treatment with ropinirole, rasagiline, rotigotine, entacapone, pramipexole, sumanirole, bromocriptine, piribedil or levodopa, with placebo as a control, on PD exhibited no significant differences on PD symptoms when the UPDRS II was used for evaluation. Moreover, using the UPDRS III, the SUCRA values indicated that a pomorphine had the best efficacy on the non-motor symptoms of PD (99.0%). Using the UPDRS II, the SUCRA values for ropinirole, rasagiline, rotigotine, entacapone, pramipexole, sumanirole, bromocriptine, piribedil and

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levodopa treatments, with placebo as a control, indicated that bromocriptine showed the best efficacy on the non-motor symptoms of PD (75.6%). **Conclusion:** Among ropinirole, rasagiline, rotigotine, entacapone, apomorphine, pramipexole, sumanirole, bromocriptine, piribedil and levodopa, with placebo as a control, apomorphine may be the most efficacious drug for therapy in treating the non-motor symptoms of PD.

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Introduction

Parkinson's disease (PD) ranks as the second most common neurodegenerative disease, second only to Alzheimer's disease. Its prevalence rate is approximately 0.3%, which increases to 1% in individuals over 60 years old [1, 2]. The clinical manifestations of PD include not only the main motor symptoms of resting tremor and slowness but also the non-motor symptoms of hyposmia, cognitive impairment and sleep disorders [3-6]. The pathogenesis of PD is not entirely clear, but it is thought to be caused by aging, genetic predisposition and exposure to environmental toxins [7]. Interestingly, the degeneration or death of substantia nigra-striatum dopamine neurons and development of eosinophilic inclusion bodies commonly occur in PD [8, 9]. At present, the treatment and management for PD involves drug therapy, surgery, cell transplantation and rehabilitation [10].

Currently, the clinical therapeutic drugs for PD are divided into symptomatic therapeutic drugs and a variety of targeted therapeutic drugs. The symptomatic therapeutic drugs mainly include levodopa (LD), a dopamine (DA) receptor agonist, monoamine oxidase (MAO-B) inhibitor and catechol-O-methyl transferase (COMT) inhibitor. LD is the most effective oral drug for PD and can complement a multi-DA neurotransmitter, reduce tremor and effectively improve slowness and stiffness [11]. DA receptors such as G protein-coupled receptors are widely distributed in body and can be divided into D1 receptors and D2 receptors according to their functional characteristics. They can expand visceral blood vessels and have diuretic and natriuretic effects [12]. MAO-B inhibitors can protect neurons by anti-oxidative stress, inhibiting synuclein aggregation and reducing apoptosis and neurotrophic effects [13, 14]. A COMT inhibitor combined with LD can extend the "on" time and shorten the "off" time [15]. The eleven therapeutic drugs of PD in the study are LD; DA agonists (ropinirole and pramipexole); DA receptor agonists (rotigotine, apomorphine, sumanirole, piribedil and bromocriptine); a COMT inhibitor (entacapone); and a highly active MAO-B inhibitor (rasagiline). Piribedil is a DA receptor agonist but has never been reported to perform better than placebo in improving motor disability in early PD patients [16]. It has been reported that patients with PD have been treated with DA agonists in an effort to reduce motor complications as well as depressive symptoms [17]. In 2011, a review suggested that piribedil, pramipexole, rotigotine, ropinirole, pramipexole extended release, pergolide, and cabergoline were efficacious as symptomatic monotherapies for motor symptoms of PD, and ropinirole prolonged release was likely efficacious [18]. There was also a study that summarized medical treatments for the most common motor and non-motor symptoms in PD [19]. In the current study, a network meta-analysis method is used for the quantitative comparison of different drug therapies for the treatment and management of PD to determine the optimal treatment and course of management for PD [20].

Materials and Methods

Literature search

PubMed, Embase and the Cochrane Library were searched from their establishment date to January 2017. A manual search was also performed for the reference lists. The search was conducted using keywords combined with free words, and the index words mainly included PD, drug therapy/medication, efficacy/effectiveness, randomized controlled trial, etc.

Inclusion and exclusion criteria

The inclusion criteria included: (1) study design: randomized controlled trial (RCT); (2) interventions: placebo, ropinirole, rasagiline, rotigotine, entacapone, apomorphine, pramipexole, sumanirole, bromocriptine, piribedil or LD; (3) study subjects: PD patients over 50 years old; and (4) outcome evaluation: United Parkinson's Disease Rating Scale (UPDRS). The exclusion criteria were as follows: (1) PD patients with mental disorders such as confusion, hallucination, delusion, excitation, delirium and abnormal behavior; (2) PD patients undergoing surgery; (3) PD patients with orthostatic hypotension; (4) PD patients with a history of epilepsy or convulsion; (5) PD patients with clinically relevant hepatic, renal or cardiac disorders; (6) PD patients who were treated with of DA receptor agonists or antipsychotic drugs; (7) studies with insufficient data; (8) non-RCTs; (9) duplicated publications; (10) conference reports, system evaluations or summary articles; and (11) non-English publications.

Data extraction and quality assessment

Two researchers extracted the data from included literature independently according to a unified data collection form. If there were disputes, a number of researchers would discuss to reach a consensus. More than two researchers used the Cochrane Collaboration's tool for assessing risk of bias in the randomized controlled trials [21]. The tool included six domains, namely, random assignment, allocation concealment, blinding, loss of outcome data, choosing the outcome reports and other biases. The evaluation included a judgment of "yes", "no", or "unclear" for each aspect to determine a low, high, or unclear risk of bias, respectively. When one or no aspects are defined as "unclear" or "no", the study has a low risk of bias. When four or more aspects are deemed "unclear" or "no", the study has a high risk of bias. If two or three aspects are deemed "unclear" or "no", the study has a moderate risk of bias [22]. Quality assessment of publication bias was performed by Review Manager 5 (RevMan 5.2.3, Cochrane Collaboration, Oxford, UK).

Statistical method

Initially, we conducted traditional pairwise meta-analyses for studies directly comparing various treatment arms. The pooled estimates of weighted mean differences (WMDs) and 95% credible intervals (CIs) of UPDRS were calculated. Chi-square tests and I-square tests were employed to examine heterogeneity among the studies [23]. Then, a network diagram was drawn by R 3.2.1 software, in which each node represented an intervention measure, the size of the node represented the sample size, and the thickness of the line between nodes represented the number of included studies. Subsequently, a Bayesian network meta-analysis was carried out to compare different interventions to each other. Each analysis was run depending on a non-informative prior for effective sizes as well as precision. Convergence and lack of autocorrelation were examined and determined following four chains and a 20,000-simulation burn-in phase. Finally, direct probability statements were determined from an additional 50,000-simulation phase [24]. To interpret WMDs, we computed the probability of each intervention being the most effective or safest treatment according to a Bayesian approach, with the help of probability values summarized as surface under the cumulative ranking curve (SUCRA). A larger the SUCRA value indicated a better rank of the intervention [25, 26]. All computations were finished by applying an R (V.3.1.2) package gemtc (V.0.6) with the Markov Chain Monte Carlo engine Open BUGS (V.3.4.0).

Results

Baseline characteristics of included publications

We retrieved 1,341 related publications in total, among which 382 duplications, 216 letters or reviews and 181 non-English publications were immediately eliminated. In the remaining 562 publications, 223 non-human publications, 142 publications unrelated to PD, 173 publications unrelated to drug therapy and 3 publications without complete data were eliminated. Finally, 21 RCTs published from 2000 to 2015 were enrolled into this network meta-analysis, including 4,844 cases of PD patients, most of whom took placebo [27-47] (Fig. 1). Among these 21 RCTs, 16 trials were performed in Caucasians, 5 trials were in Asians, while 18 trials were two-arm, and 3 trials were three-arm. The baseline characteristics of included publications are shown in Table 1 and Table 2, and the Cochrane bias evaluation is shown in Fig. 2.

Table 1. The baseline characteristics of included studies. Note: D, drug; M, male; F, female; NR, not report; A = Placebo; B = Ropinirole; C = Rasagiline; D = Rotigotine; E = Entacapone; F = Apomorphine; G = Pramipexole; H = Sumanitrole; I = Bromocriptine; J = Piribedil; K = Levodopa

First author	Year	Ethnicity	Treatments			Sample size			Disease duration (years)			Hoehn and Yahr stage	Baseline UPDRS (II/III)			Treatment duration	Dose of drug	
			D1	D2	D3	D1	D2	D3	D1	D2	D3		D1	D2	D3			
Smith KM [27]	2015	Caucasians	A	C	-	192	99	93	-	NR	NR	NR	6.1/15.0	5.9/14.6		36-week	1 or 2mg/d	
Nomoto M [28]	2014	Asians	A	D	-	172	86	76	-	5.4±3.0	7.5±6.0	II-IV	10.3/26.2	11.8/28.1		19-week	2-16 mg/d	
Nicholas AP [29]	2014	Caucasians	A	D	-	208	101	107	-	≥3	≥3	II-IV	12.8/26.1	11.8/23.1		16-week	4 mg/d	
Ray Chaudhuri K [30]	2013	Caucasians	A	D	-	267	89	178	-	NR	NR	I-IV	NR/31.8	NR/29.7		12-week	2-16 mg/d	
Mizuno Y [31]	2013	Asians	A	D	-	176	88	88	-	1.8±1.9	2.0±1.8	I-III	7.4/28.2	6.8/20.2		19-week	2-16 mg/d	
Grosset KA-a [32]	2013	Caucasians	A	F	-	47	15	32	-	5	5	II-IV	NR/21.1	NR/25.7		20-week	1.5-4 mg/d	
Grosset KA-b [33]	2013	Caucasians	A	F	-	55	15	40	-	11.5±3.2	12.2±3.9	II-IV	NR	NR		17-week	1.5-4.5 mg/d	
Stocchi F [34]	2011	Caucasians	A	C	E	105	37	32	36	10.7±5.8	10.2±4.5	9.4±3.7	II-IV	18.8/40.3	17.5/38.0	18.3/39.4	30-week	1/200mg/d
Watts RL [35]	2010	Caucasians	B	K	-	208	104	104	-	2.7±2.1	2.7±2.4	I-III	8.6/19.6	8.2/19.4		104-week	2-24/50-1000mg/d	
Hauser RA [36]	2010	Caucasians	A	G	-	156	50	106	-	0.8±1.1	1.1±1.3	I-III	7.6/22.4	7.9/22.6		18-week	0.375-4.5 mg/d	
Singer C [37]	2007	Caucasians	A	B	H	609	203	202	204	1.38±0.13	1.23±0.10	1.37±0.11	I-III	8.5/20.4	8.1/19.1	9.1/21.1	40-week	0.75-24/1-16 mg/d
Mizuno Y [38]	2007	Asians	A	B	-	241	120	121	-	5.5±4.1	5.5±3.7	II-IV	NR/24.9	NR/23.8		16-week	0.75-15 mg/d	

Table 2. The baseline characteristics of included studies. Note: D, drug; M, male; F, female; NR, not report; A = Placebo; B = Ropinirole; C = Rasagiline; D = Rotigotine; E = Entacapone; F = Apomorphine; G = Pramipexole; H = Sumanitrole; I = Bromocriptine; J = Piribedil; K = Levodopa

First author	Year	Ethnicity	Treatments			Sample size			Disease duration (years)			Hoehn and Yahr stage	Baseline UPDRS (II/III)			Treatment duration	Dose of drug	
			D1	D2	D3	Total	D1	D2	D3	D1	D2		D3	D1	D2			D3
Jankovic J [39]	2007	Caucasians	A	D	-	277	96	181	-	5	5	I-III	8.7/21.3	8.3/21.6		32-week	2,4,or 6 mg/d	
Castro-Caldas A [40]	2006	Caucasians	I	J	-	425	215	210	-	3.3±2.4	3.1±2.0	I-III	9.2/24.1	9.3/23.8		48-week	1.25-25/50-150 mg/d	
Reichmann H [41]	2005	Caucasians	A	E	-	270	96	174	-	7.1±4.0	7.5±4.7	I-IV	24.7/38.6	23.5/37.6		13-week	200mg/d	
Rascol O [42]	2005	Caucasians	A	C	E	687	229	231	227	8.8±4.8	8.7±4.9	9.2±4.7	NR	18.9/23.7	19.0/24.0	19.1/23.1	18-week	1/200mg/d
Wong KS [43]	2003	Asians	A	G	-	150	77	73	-	4.3±0.4	4.5±0.4	I-IV	10.8/26.6	10.7/26.7		15-week	0.375-4.5 mg/d	
Im JH [44]	2003	Asians	B	I	-	76	37	39	-	6.8±3.8	6.4±3.2	II-IV	NR/19	NR/21.8		16-week	0.75-9.0/1.25-17.5 mg/d	
Brooks DJ [45]	2003	Caucasians	A	E	-	172	57	115	-	9.1±5.3	9.6±5.1	NR	9.4/22.4	10.3/23.4		24-week	200mg/d	
Pogarell O [46]	2002	Caucasians	A	G	-	83	39	44	-	6.0±3.5	6.5±4.0	I-IV	11.5/32.1	13.0/34.2		12-week	0.375-4.5 mg/d	
Rascol O [47]	2000	Caucasians	B	K	-	268	179	89	-	2.5±2.8	2.4±2.3	I-III	8.0/21.5	8.0/21.7		NR	0.75-24/50-1200mg/d	

Fig. 2. Cochrane system bias evaluations for each of included publications.

Pairwise meta-analysis of the efficacies of ten drugs on PD

As in shown in Table 3, direct pairwise comparison of the efficacies of ten drugs for PD found that, according to the UPDRS III, the efficacy of placebo in treating PD was worse than those of apomorphine and sumanirole (WMD = -10.37, 95% CI = -15.72~-5.02; and WMD = -0.60, 95% CI = -0.66~-0.54, respectively) but was better than that of ropinirole (WMD = 0.40, 95% CI = 0.34~0.46). Compared with sumanirole, ropinirole exhibited lower efficacy (WMD = -1.00, 95% CI = -1.06~-0.94). Using the UPDRS II, placebo and ropinirole showed lower efficacy than sumanirole (WMD = -0.60, 95% CI = -0.66~-0.54; and WMD = -1.00, 95% CI = -1.06~-0.94, respectively), but placebo had a better efficacy than ropinirole (WMD = 0.40, 95% CI = 0.34~0.46).

Evidence of a network relationship

Using the UPDRS III and UPDRS II, we found that most PD patients took placebo, and the majority of direct pairwise comparisons refer to placebo vs. rasagiline, placebo vs. rotigotine, placebo vs. entacapone and placebo vs. pramipexole (Fig. 3).

The main results of the network meta-analysis of the efficacies of ten drugs on PD

The main results of the network meta-analysis showed that, using the UPDRS III, apomorphine presented better efficacy than placebo, ropinirole, rasagiline, rotigotine, entacapone, pramipexole, sumanirole and LD (WMD = -10.90; 95% CI = -16.12~-5.48; WMD = -11.85; 95% CI = -17.31~-6.16; WMD = -11.15, 95% CI = -16.64~-5.04; WMD = -11.70, 95% CI = -16.98~-5.60; WMD = -11.04, 95% CI = -16.97~-5.34; WMD = -13.27, 95% CI = -19.22~-7.40; WMD = -10.25, 95% CI = -15.66~-4.32; and WMD = -11.60, 95% CI = -17.89~-5.57, respectively) Table 4 and Fig. 4). However, when using the UPDRS II, the treatment of PD of using ropinirole, rasagiline, rotigotine, entacapone, pramipexole, sumanirole, bromocriptine, piribedil and LD, with placebo as a control, showed no significant differences in efficacy (Table 5).

Table 3. Pairwise meta-analysis of based on Unified Parkinson's Disease Rating Scale (UPDRS) III and UPDRS II. Note: WMD, weighted mean difference; CI, confidence intervals; NA, not available; UPDRS, Unified Parkinson's Disease Rating Scale; A = Placebo; B = Ropinirole; C = Rasagiline; D = Rotigotine; E = Entacapone; F = Apomorphine; G = Pramipexole; H = Sumanirole; I = Bromocriptine; J = Piribedil; K = Levodopa

Included studies	Comparisons	Pairwise meta-analysis		
		WMD (95%CI)	I ²	P
UPDRS III				
1 study	A vs. B	0.40(0.34~0.46)	NA	NA
3 studies	A vs. C	0.13(-0.60~0.87)	0.00%	0.766
5 studies	A vs. D	2.48(-2.14~7.11)	96.20%	<0.001
3 studies	A vs. E	-0.81(-2.07~0.44)	0.00%	0.774
2 studies	A vs. F	-10.37(-15.72~-5.02)	0.00%	0.691
3 studies	A vs. G	4.00(-4.36~12.36)	84.70%	0.001
1 study	A vs. H	-0.60(-0.66~-0.54)	NA	NA
1 study	B vs. H	-1.00(-1.06~-0.94)	NA	NA
1 study	B vs. I	-4.20(-9.17~0.77)	NA	NA
2 studies	B vs. K	0.28(-1.00~1.56)	0.00%	0.709
2 studies	C vs. E	-0.89(-2.19~0.42)	0.00%	0.958
1 study	I vs. J	0.50(-0.42~1.42)	NA	NA
UPDRS II				
1 study	A vs. B	0.40(0.34~0.46)	NA	NA
3 studies	A vs. C	0.13(-0.60~0.87)	0.00%	0.766
3 studies	A vs. D	3.20(-3.64~10.03)	98.00%	<0.001
4 studies	A vs. E	0.33(-1.69~2.35)	45.20%	0.088
3 studies	A vs. G	4.00(-4.36~12.36)	84.70%	0.001
1 study	A vs. H	-0.60(-0.66~-0.54)	NA	NA
1 study	B vs. H	-1.00(-1.06~-0.94)	NA	NA
1 study	B vs. I	-4.20(-9.17~0.77)	NA	NA
2 studies	B vs. K	0.17(-0.47~0.80)	0.00%	0.95
2 studies	C vs. E	1.61(-2.79~6.02)	96.80%	<0.001
1 study	I vs. J	0.50(-0.42~1.42)	NA	NA

Cumulative probability of sorting

Using the UPDRS III, the SUCRA values for ropinirole, rasagiline, rotigotine, entacapone, apomorphine, pramipexole, sumanirole, bromocriptine, piribedil and LD, with placebo as a control, showed that apomorphine exhibited the best efficacy (90%), but pramipexole presented the worst efficacy (8.7%) (Fig. 5A). Using the UPDRS II, the SUCRA values for ropinirole, rasagiline, rotigotine, entacapone, pramipexole, sumanirole, bromocriptine, piribedil and LD, with placebo as a control, demonstrated that the efficacy of bromocriptine on PD was the best (75.6%), while the efficacy of rotigotine on PD was the worst (22.0%) (Fig. 5B).

Discussion

The network meta-analysis method was used to evaluate differences in efficacy for ropinirole, rasagiline, rotigotine, entacapone, apomorphine, pramipexole, sumanirole, bromocriptine, pPiribedil and LD, with placebo as a control, in the treatment and management of PD.

The direct comparison of pairwise meta-analysis showed that the efficacy of apomorphine and sumanirole for treating PD were better than other drugs. The probable reason is that the main pathological changes of PD patients are the degeneration or loss of neuronal tissue and the decrease of striatal DA neurotransmitter. Both apomorphine and sumanirole are DA receptor activators. They have a long half-life and can remain in the blood to improve the dyskinesia induced by long-term use of LD and reduce the severity of the “on-off” effect [48]. Moreover, the DA receptor activators apomorphine and sumanirole can stimulate the viable DA receptors to

Fig. 3. Network evidence diagrams of the efficacy of ten drugs for Parkinson's disease using the United Parkinson's Disease Rating Scale (UPDRS) III and the UPDRS II of Parkinson's disease. (Note: A = UPDRS III; B = UPDRS II).

Table 4. Primary outcomes of UPDRSIII improvements. Notes: UPDRS, Unified Parkinson's Disease Rating Scale; bold numbers represent the differences are of significances

Placebo	-0.91 (-2.88, 1.00)	-0.25 (-2.17, 1.71)	-0.70 (-2.37, 0.92)	-0.29 (-2.42, 2.03)	10.90 (5.48, 16.12)	-2.56 (-5.33, 0.43)	0.69 (-1.62, 3.01)	3.72 (-2.17, 9.11)	3.50 (-3.23, 9.52)	-0.78 (-4.12, 2.24)
0.91 (-1.00, 2.88)	Ropinirole	0.64 (-1.95, 3.39)	0.23 (-2.40, 2.73)	0.63 (-2.19, 3.61)	11.85 (6.16, 17.31)	-1.62 (-4.94, 1.92)	1.62 (-0.68, 3.93)	4.59 (-0.91, 9.95)	4.41 (-1.97, 10.31)	0.13 (-2.50, 2.65)
0.25 (-1.71, 2.17)	Rasagiline	-0.64 (-3.39, 1.95)	-0.50 (-2.96, 2.09)	-0.02 (-2.41, 2.37)	11.15 (5.04, 16.64)	-2.37 (-5.62, 1.18)	0.96 (-2.00, 3.84)	3.95 (-2.52, 9.71)	3.74 (-3.43, 10.27)	-0.51 (-4.35, 2.96)
0.70 (-0.92, 2.37)	Rotigotine	-0.23 (-2.73, 2.40)	0.50 (-2.09, 2.96)	0.38 (-2.33, 3.21)	11.70 (5.60, 16.98)	-1.83 (-5.10, 1.62)	1.41 (-1.48, 4.23)	4.41 (-1.88, 10.12)	4.24 (-2.80, 10.45)	-0.07 (-3.84, 3.46)
0.29 (-2.03, 2.42)	Entacapone	-0.63 (-3.61, 2.19)	0.02 (-2.37, 2.41)	-0.38 (-3.21, 2.33)	11.04 (5.34, 16.97)	-2.21 (-5.77, 1.43)	1.01 (-2.25, 4.03)	4.13 (-2.53, 9.91)	3.95 (-3.49, 10.46)	-0.53 (-4.59, 3.11)
-10.90 (-16.12, -5.48)	Apomorphine	-11.85 (-17.31, -6.16)	-11.15 (-16.64, -5.04)	-11.70 (-16.98, -5.60)	-11.04 (-16.97, -5.34)	-13.27 (-19.22, -7.40)	-10.25 (-15.66, -4.32)	-7.05 (-15.18, 1.74)	-7.10 (-16.27, 1.64)	-11.60 (-17.89, -5.57)
2.56 (-0.43, 5.33)	Pramipexole	1.62 (-1.92, 4.94)	2.37 (-1.18, 5.62)	1.83 (-1.62, 5.10)	2.21 (-1.43, 5.77)	13.27 (7.40, 19.22)	3.25 (-0.49, 6.78)	6.10 (-0.58, 12.91)	5.96 (-1.41, 13.03)	1.80 (-3.00, 5.81)
-0.69 (-3.01, 1.62)	Sumanitrole	-1.62 (-3.93, 0.68)	-0.96 (-3.84, 2.00)	-1.41 (-4.23, 1.48)	-1.01 (-4.03, 2.25)	10.25 (4.32, 15.66)	-3.25 (-6.78, 0.49)	3.01 (-2.99, 8.59)	2.84 (-4.00, 9.02)	-1.45 (-5.01, 1.76)
-3.72 (-9.11, 2.17)	Bromocriptine	-4.59 (-9.95, 0.91)	-3.95 (-9.71, 2.52)	-4.41 (-10.12, 1.88)	-4.13 (-9.91, 2.53)	7.05 (-1.74, 15.18)	-6.10 (-12.91, 0.58)	-3.01 (-8.59, 2.99)	-0.12 (-3.13, 2.83)	-4.63 (-10.61, 1.63)
-3.50 (-9.52, 3.23)	Piribedil	-4.41 (-10.31, 1.97)	-3.74 (-10.27, 3.43)	-4.24 (-10.45, 2.80)	-3.95 (-10.46, 3.49)	7.10 (-1.64, 16.27)	-5.96 (-13.03, 1.41)	-2.84 (-9.02, 4.00)	0.12 (-2.83, 3.13)	-4.46 (-10.96, 2.55)
0.78 (-2.24, 4.12)	Levodopa	-0.13 (-2.65, 2.50)	0.51 (-2.96, 4.35)	0.07 (-3.46, 3.84)	0.53 (-3.11, 4.59)	11.60 (5.57, 17.89)	-1.80 (-5.81, 3.00)	1.45 (-1.76, 5.01)	4.63 (-1.63, 10.61)	4.46 (-2.55, 10.96)

Fig. 4. The relative relationship forest plots of the efficacy of ten drugs for Parkinson's disease using the United Parkinson's Disease Rating Scale (UPDRS) III. (Note: A = placebo; B = ropinirole; C = rasagiline; D = rotigotine; E = entacapone; F = apomorphine; G = pramipexole; H = sumanitrole; I = bromocriptine; J = piribedil; K = levodopa).

down-regulate the expression of the apoptotic protein Bax and up-regulate the expression of the anti-apoptosis protein Bcl-2 [49]. This will indirectly increase the number of neurons, inhibit the abnormal accumulation caused by amyloid filaments of α -synuclein conformational change, delay the development of early symptoms of PD and improve depression symptoms of PD patients [50].

The results of this network meta-analysis further showed that, according to analysis using the UPDRS III, the efficacy of apomorphine was the best among the eleven drugs examined. The reasons are as follows: First, apomorphine can improve the number and activity of DA neurons, which will alleviate the memory disorder seen in PD patients [51]. Moreover, apomorphine can reduce glucose metabolism in the left frontal region and, at the same time, increase glucose metabolism in right occipital temporal region. This will positively regulate the motor function and mood of PD patients and change the motor, cognitive, and motivational state of brain regions in PD patients to improve their quality of life [52, 53]. Second, apomorphine may alter the expression of important early PD-

Table 5. Primary outcomes of UPDRS II improvements. Notes: UPDRS, Unified Parkinson's Disease Rating Scale

Placebo	-0.34 (-8.83, 7.77)	-0.64 (-5.44, 4.17)	-3.19 (-8.18, 1.89)	-0.28 (-4.57, 4.08)	-2.26 (-7.70, 2.65)	0.60 (-8.07, 8.94)	3.79 (-8.82, 16.71)	3.31 (-11.77, 19.06)	-0.37 (-10.90, 9.91)
0.34 (-7.77, 8.83)	Ropinirole	-0.34 (-9.70, 9.48)	-2.82 (-12.31, 7.17)	0.03 (-9.13, 9.58)	-1.93 (-11.93, 7.88)	0.97 (-7.63, 9.45)	4.17 (-5.53, 14.21)	3.58 (-9.09, 16.80)	-0.03 (-6.28, 6.06)
0.64 (-4.17, 5.44)	0.34 (-9.48, 9.70)	Rasagiline	-2.55 (-9.60, 4.58)	0.40 (-5.13, 5.57)	-1.57 (-8.90, 5.13)	1.17 (-8.89, 11.04)	4.47 (-9.15, 18.31)	3.96 (-12.14, 20.47)	0.21 (-11.18, 11.61)
3.19 (-1.89, 8.18)	2.82 (-7.17, 12.31)	2.55 (-4.58, 9.60)	Rotigotine	2.88 (-3.69, 9.52)	0.89 (-6.46, 7.87)	3.79 (-6.29, 13.56)	7.00 (-6.68, 20.89)	6.48 (-9.67, 22.52)	2.81 (-8.95, 13.98)
0.28 (-4.08, 4.57)	-0.03 (-9.58, 9.13)	-0.40 (-5.57, 5.13)	-2.88 (-9.52, 3.69)	Entacapone	-2.00 (-8.89, 4.58)	0.86 (-8.89, 10.17)	4.05 (-9.10, 17.82)	3.58 (-12.16, 19.57)	-0.17 (-11.65, 10.76)
2.26 (-2.65, 7.70)	1.93 (-7.88, 11.93)	1.57 (-5.13, 8.90)	-0.89 (-7.87, 6.46)	2.00 (-4.58, 8.89)	Pramipexole	2.89 (-6.83, 12.74)	6.09 (-7.56, 20.28)	5.46 (-10.47, 22.30)	1.84 (-9.58, 13.62)
-0.60 (-8.94, 8.07)	-0.97 (-9.45, 7.63)	-1.17 (-11.04, 8.89)	-3.79 (-13.56, 6.29)	-0.86 (-10.17, 8.89)	-2.89 (-12.74, 6.83)	Sumanirole	3.27 (-9.47, 16.47)	2.74 (-12.52, 18.72)	-0.99 (-11.54, 9.67)
-3.79 (-16.71, 8.82)	-4.17 (-14.21, 5.53)	-4.47 (-18.31, 9.15)	-7.00 (-20.89, 6.68)	-4.05 (-17.82, 9.10)	-6.09 (-20.28, 7.56)	-3.27 (-16.47, 9.47)	Bromocriptine	-0.55 (-8.96, 8.11)	-4.24 (-15.97, 7.38)
-3.31 (-19.06, 11.77)	-3.58 (-16.80, 9.09)	-3.96 (-20.47, 12.14)	-6.48 (-22.52, 9.67)	-3.58 (-19.57, 12.16)	-5.46 (-22.30, 10.47)	-2.74 (-18.72, 12.52)	0.55 (-8.11, 8.96)	Piribedil	-3.71 (-18.39, 10.87)
0.37 (-9.91, 10.90)	0.03 (-6.06, 6.28)	-0.21 (-11.61, 11.18)	-2.81 (-13.98, 8.95)	0.17 (-10.76, 11.65)	-1.84 (-13.62, 9.58)	0.99 (-9.67, 11.54)	4.24 (-7.38, 15.97)	3.71 (-10.87, 18.39)	Levodopa

related genes. For example, it can stimulate neurotransmitters or neuromodulators in the brain to act on the Jun protein of the postsynaptic membrane, improve the transcription efficiency of downstream genes by activating the expression of AP-1 and CRE promoting factors, and directly assess the degree of the damage to neurons [54]. Lastly, the increase of Fos protein expression is an important manifestation of neuronal vitality, which can inhibit the increase of tumor necrosis factor, glial-derived neurotrophic factor and cyclinB2 mRNA, further inhibiting striatal neurodegeneration and improving resistance to infection and neurotrophic activity [55, 56]. However, apomorphine will easily degrade under light, and it can inhibit the central nervous system, which causes persistent vomiting, shortness of breath, respiratory depression, acute circulatory failure, coma, death and eosinophilia. Bradycardia and hypotension can occur 5-10 min after treatment and can even progress to acute circulatory failure [53, 57].

The SUCRA values showed that the efficacy of apomorphine was the best of the above ten drugs, which was consistent with the results of the network meta-analysis. Among the remaining nine drugs (ropinirole, rasagiline, rotigotine, entacapone, pramipexole, sumanirole, bromocriptine, piribedil and LD, with placebo as a control), the efficacy of bromocriptine on PD was the best. The probable reason is that bromocriptine, at low doses, can preferentially activate presynaptic DA receptors and combine with the activation and antagonistic parts of DA receptors [58]. Bromocriptine can also activate synaptic auto-receptors to sustain the normal function of the receptors, reducing the volatility of symptoms and improving the exercise capacity of patients with PD [59]. As a short-acting receptor agonist, apomorphine could be improved the activity to induce rotational behavior in rodent under stimulation of Hydrogen sulfide [60].

This study used a Bayesian network model to match the direct evidence and indirect evidence in the 21 RCTs while comparing the efficacy of ten drugs in treating PD. The network meta-analysis is a statistical method that can perform quantitative comparisons of different interventions intended to treat the same disease. Its biggest benefit is that it can also sort comparisons according to indexes to choose the best treatment plan [61]. This study has clinical guiding significance for the treatment of PD. Regarding inclusion criteria, the UPDRS has both strengths and weaknesses; however, a study confirmed the decision to prioritize the UPDRS as the first Task Force assessment [62]. MDS-UPDRS has reported excellent factor validity [63]. However, the MDS-UPDRS takes a long time, which causes difficulty in clinical and research settings [64]. The included articles used the UPDRS as the inclusion criteria,

except one article using both UPDRS and MDS-UPDRS. Therefore, in this study, we took the UPDRS as our inclusion criteria. The dosages of drugs were as follows: ropinirole was 0.75-24 mg/d, rasagiline was 1 or 2 mg/d, rotigotine was 2-16 mg/d, entacapone was 200 mg/d, apomorphine was 1.5-4.5 mg/d, pramipexole was 0.375-4.5 mg/d, sumanirole was 1-16 mg/d, bromocriptine was 1.25-25 mg/d, piribedil was 50-150 mg/d, and LD was 50-1200 mg/d. Drugs in each article were at the same dosages, therefore the dosage should not affect our results. The sample sizes of the ten interventions were different and the number of included pairwise comparisons was different, so those factors could affect the research results. The improvement of the UPDRS III was used to evaluate the efficacy of ten drugs for treating PD, while the improvement of the UPDRS II was used to evaluate the efficacy of nine drugs for treating PD. The unequal number of interventions prevented cluster analysis, which would have likely resulted in different research results.

Above all, our results showed that, among ropinirole, rasagiline, rotigotine, entacapone, apomorphine, pramipexole, sumanirole, bromocriptine, piribedil and LD, with placebo as a control, apomorphine may be the most efficacious drug therapy for PD. From Table 1 and Table 2, we can see that there are no significant differences in the disease duration, Hoehn & Yahr scores (disease stage), pretreatment UPDRS, treatment duration or baseline UPDRS (II/III) scores. However, due to a few articles without specific values, we could not do a meta-regression or a subgroup analysis. Larger sample sizes are needed to confirm the findings of this meta-analysis.

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Disclosure Statement

There are no conflicts of interest to declare for this paper.

Fig. 5. The cumulative ranking probability diagram of the efficacy of ten drugs for Parkinson's disease using the United Parkinson's Disease Rating Scale (UPDRS) III and the UPDRS II of Parkinson's disease. (Note: A = UPDRS III; B = UPDRS II).

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