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Review Article

Efficacy and safety of pramipexole in Parkinson's disease with anxiety or depression: a meta-analysis of randomized clinical trials

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Abstract: Background: To investigate the efficacy and safety of pramipexole in Parkinson's disease with anxiety or depression by analyzing the randomized clinical trials (RCTs). Methods: National Library of Medicine (PubMed), Cochrane Library of EMBASE, CNKI, VIP and Wanfang database were retrieved to conduct a meta-analysis. We performed sensitivity analysis to assess the efficacy and safety of pramipexole in Parkinson's disease with anxiety or depression. Results: In our study, the results showed that the efficiency was significantly improved in patients with Parkinson's disease of the experimental group (fixed effect model, SMD = 3.45, 95% CI = [2.50, 4.76]). The HAMD score of experimental group was lower than that of control group. Moreover, adverse events of experimental group were lower than that of control group. Conclusions: The research demonstrated_that pramipexole may improve the efficacy and HAMD score of Parkinson's disease with anxiety or depression. Due to the limited number of included studies, more RCTs are needed to investigate the effect of pramipexole in Parkinson's disease with anxiety or depression.

Keywords: Pramipexole, anxiety, depression, Parkinson's disease, efficacy, safety, RCTs, meta-analysis

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease which involves a wide range of motor and non-motor symptoms [1, 2]. It will eventually lead to severe disability, and thus a very poor health-related quality of life (HRQOL) of elderly people [3-5]. Epidemiological studieshave shownthat the incidence of depression or anxiety was high among the PD population [6]. Its incidence is up to 40%, which can occur at all stages of PD, and even before exercise symptoms [7]. Leentjens et al. [8] found that old age, female, physical complications and family history of depression were the risk factors.

Pramipexole is a commonly used dopamine receptor agonist in clinic [9]. Many studies have demonstrated that pramipexole has antidepressant effect [10-15]. Barone et al. [16] conducted a 12-week randomized controlled double-blind trial in patients with Parkinson's disease and depression from 76 research centers in Europe and South Africa. The change of Beck Depression Scale score was used as the main outcome indicator, the results showed that pramipexole group (0.125-1.0 mg tid) had an average decrease of 5.9%, while the average decrease in the control group was 3.2% (P = 0.01). However, no systematic studies have indicated whether pramipexole could improve Parkinson's disease with anxiety or depression.

This study aimed to assess the effects and safety of pramipexole in Parkinson's disease with anxiety or depression.

Materials and methods

Search strategy

In this study, the retrieval language was limited to Chinese and English, and the latest retrieval time was up to April 2021. The Chinese databases mainly include CNKI, VIP, Wanfang and related Chinese search engines; English data-

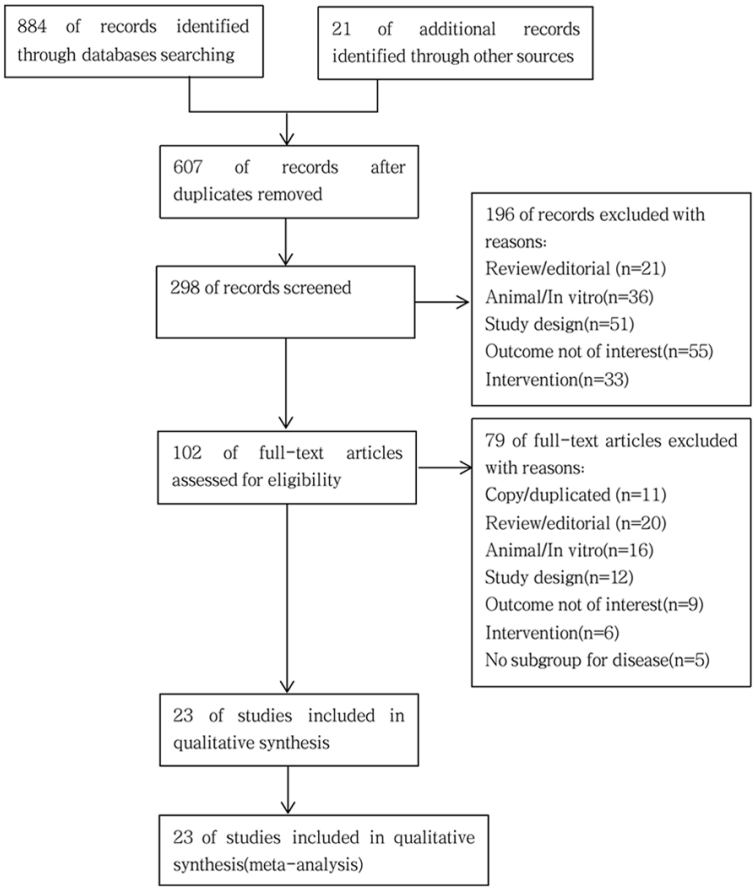

Figure 1. Flow diagram of the literature search.

bases mainly include PubMed, EMBASE, Cochrane Library, ScienceDirect and related English search engines. At the same time, we also traced the references of the retrieved literature again, in order to ensure the comprehensiveness of the retrieval. The key words for retrieval are shown as follows: ((“Pramipexole”) AND (“Parkinson’s disease”) AND (“anxiety” OR “Depression”)).

Inclusion and exclusion criteria

Inclusion criteria: (a) Literature involving pramipexole in the treatment of PD patients with depression or anxiety; (b) The main outcome measures were HAMD score and clinical effective rate after treatment, and the secondary outcome measures were the incidence of adverse reactions; (c) RCTs.

Exclusion criteria: (a) Observational study; (b) Animal research; (c) Documents with poor quality or repetitive research, too little reported information, and unusable data; (d) Severe mental illness, heart, liver and other major organ diseases cannot be evaluated.

Data extraction and quality assessment

Two researchers independently extracted the data, including the first author, year of publication, sample size, intervention measures, control measures, effective number of clinical treatments, number of adverse reactions, HAMD score after treatment, etc. The total score was 0-7. The total score of 0-3 indicates low-quality research and 4-7 indicates high-quality research. In case of disagreement, it shall be settled through discussion or arbitration by a third-party researcher.

Statistical analysis

Review Manager Software (RevMan, version 5.2 from the Cochrane Collaboration) was used for data analysis and statistics of all outcome indicators. According to the heterogeneity test results, the effect model was determined. $I^2 \geq 50\%$ indicated greater heterogeneity, and the random effect model (RE) was selected; $I^2 \leq 50\%$ indicated that the heterogeneity was within the acceptable range, and the fixed effect model (FE) was selected. Continuous variables were combined with weighted mean difference (WMD), and binary variables were combined with RR. When $P<0.05$, it was considered that there were significant differences in the changes of each outcome index. Subgroup analysis was used to identify the source of heterogeneity, and sensitivity analysis was used to assess the impact of individual studies on the overall results.

Results

Flow chart of study selection

A total of 884 articles were screened in Chinese database and English database by using preset measurement and keywords. After software

Table 1. Characteristics of the 23 studies in the meta-analysis

Author Year	Country	Size EG/ CG	Types of studies and intervention	Doses	Therapy (months)
Li 2014 [17]	China	40/40	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3
Zhang 2012 [18]	China	27/27	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	2
Lin 2014 [19]	China	40/39	RCT comparing the use of pramipexole	Pramipexole 0.25 mg QD	3
Dai 2010 [20]	China	25/22	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3
Zhu 2016 [21]	China	60/60	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3
Li Jie 2014 [22]	China	60/60	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	2
Gao 2015 [23]	China	50/50	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3
Qiao 2011 [24]	China	28/28	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3
Zhu 2013 [25]	China	45/45	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3
Chen 2016 [26]	China	41/41	RCT comparing the use of pramipexole	Pramipexole 0.25 mg QD	3
Li 2016 [27]	China	66/66	RCT comparing the use of pramipexole	Pramipexole 0.25 mg QD	3
Li Hua li 2014 [28]	China	30/30	RCT comparing the use of pramipexole	Pramipexole 0.25 mg QD	3
Su 2010 [29]	China	25/25	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3
Fang 2011 [30]	China	23/23	RCT comparing the use of pramipexole	Pramipexole 0.25 mg QD	3
Deng 2014 [31]	China	32/32	RCT comparing the use of pramipexole	Pramipexole 0.25 mg QD	3
Ma 2011 [32]	China	27/26	RCT comparing the use of pramipexole	Pramipexole 0.25 mg QD	3
Wu 2016 [33]	China	23/23	RCT comparing the use of pramipexole	Pramipexole 0.25 mg QD	3
Zhu 2014 [34]	China	20/25	RCT comparing the use of pramipexole	Pramipexole 0.25 mg QD	3
Zhang 2010 [35]	China	21/25	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3
Barone 2010 [16]	American	144/152	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3
Barone 2006 [36]	American	33/34	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3
Tian 2019 [37]	China	60/60	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3
Man 2018 [38]	China	34/34	RCT comparing the use of pramipexole	Pramipexole 0.125 mg tid	3

analysis, 607 repetitive literatures were excluded and 163 were left. After reading the full text of the literature, 79 articles that did not meet the inclusion criteria were excluded, and then further analysis of the literature data was carried out. The papers with low statistical quality were excluded, remaining 2 articles in English [16, 36] and 21 articles in Chinese [17-35, 37, 38], a total of 23 articles (**Figure 1**) were included in this Meta-analysis.

Characteristics of included studies

The characteristics of included studies are summarized in **Table 1**. Twenty-three RCTs involving pramipexole in the treatment of PD with anxiety or depression were included. The course of treatment of two RCTs [18, 22] was 8 weeks, while the others [16, 17, 19-21, 23-38] were 12 weeks or 3 months. All the experimental groups were treated with pramipexole [16-38]. 13 RCTs [17, 21-23, 25-27, 29, 30, 34, 36-38] counted the number of effective cases; The HAMD scores after 12 weeks or 3 months of treatment were calculated in 15 RCTs [17, 19-24, 28-35]; 11 RCTs [16, 18, 19, 27, 28, 30-33, 36, 38] counted the number of adverse events. The literature was reported from year 1999 to 2021. **Figure 2** shows the risk of bias of RCTs. All RCTs were with an unclear risk of other bias. In summary, the quality of these studies was moderate to high.

Pooled analysis

The effect of pramipexole in Parkinson's disease with anxiety or depression: Meta-analysis of data from the 13 eligible studies [17, 21-23, 25-27, 29, 30, 34, 36-38] showed that efficiency were significantly improved in the experimental group (fixed effect model, SMD = 3.45, 95% CI = [2.50, 4.76]; **Figure 3**).

The HAMD score of pramipexole in Parkinson's disease with anxiety or depression: We conducted a forest plot for the HAMD score of pramipexole in Parkinson's disease with anxiety or depression. 15 included studies [17, 19-24, 28-35] reported the results of HAMD score. There were 504 cases in the experimental group and 508 cases in the control group.

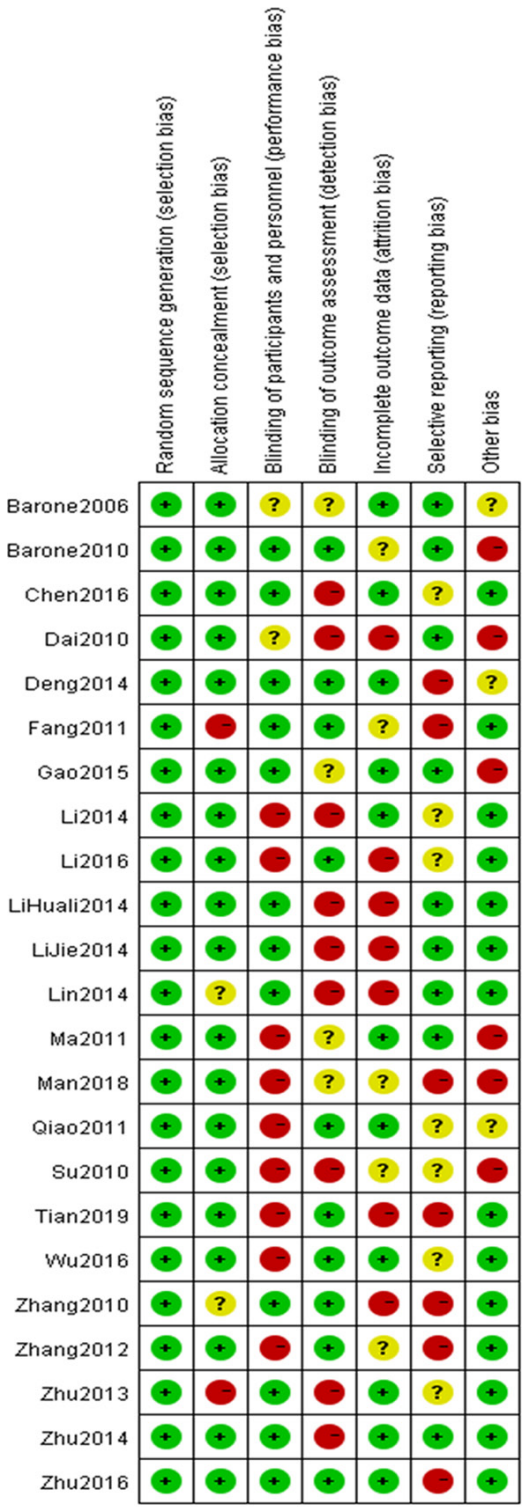

Figure 2. The risk of bias of randomized trials included in the meta-analysis.

Meta-analysis showed that HAMD score of experimental group was lower than that of control group. In experimental Group [WMD = -3.24, 95% CI (-3.58, -2.90), P<0.00001], the improvement of HAMD score was more obvious after pramipexole treatment, shown in **Figure 4**.

The adverse events of pramipexole in Parkinson's disease with anxiety or depression: We did a forest plot for the adverse events of pramipexole. 11 included studies [16, 18, 19, 27, 28, 30-33, 36, 38] reported the results of adverse events. There were 479 cases in the experimental group and 486 cases in the control group. Meta-analysis showed that adverse events of experimental group were lower than that of control group. In experimental Group [WMD = -0.07, 95% CI (-0.12, -0.02), P = 0.006], the decrease of adverse events was more obvious after pramipexole treatment, shown in **Figure 5**.

Sensitivity analysis and publication bias

Sensitivity analysis revealed that removal of any one study from the analysis did not subvert the results of the pooled analysis (data not shown). The funnel plots (**Figure 6**) demonstrated there was no publication bias.

Discussion

In this study, we showed that the efficiency was significantly improved in the experimental group (fixed effect model, SMD = 3.45, 95% CI = [2.50, 4.76]). The HAMD score of experimental group was lower than that of control group, and the improvement of HAMD score was more obvious after pramipexole treatment in the experimental Group [WMD = -3.24, 95% CI (-3.58, -2.90), P<0.00001]. Moreover, adverse events of experimental group were lower than that of control group, and the decrease of adverse events was more obvious after pramipexole treatment. The funnel plots showed no publication bias.

Twenty-three RCTs were included in this study, which were moderate to high quality. The combined results showed that pramipexole had more significant improvement in depression or anxiety in patients with Parkinson's disease, and significantly decreased adverse events. At present, there are few large-scale clinical trials of pramipexole in the treatment of Parkinson's disease with anxiety or depression. Therefore, more studies are needed to research the mech-

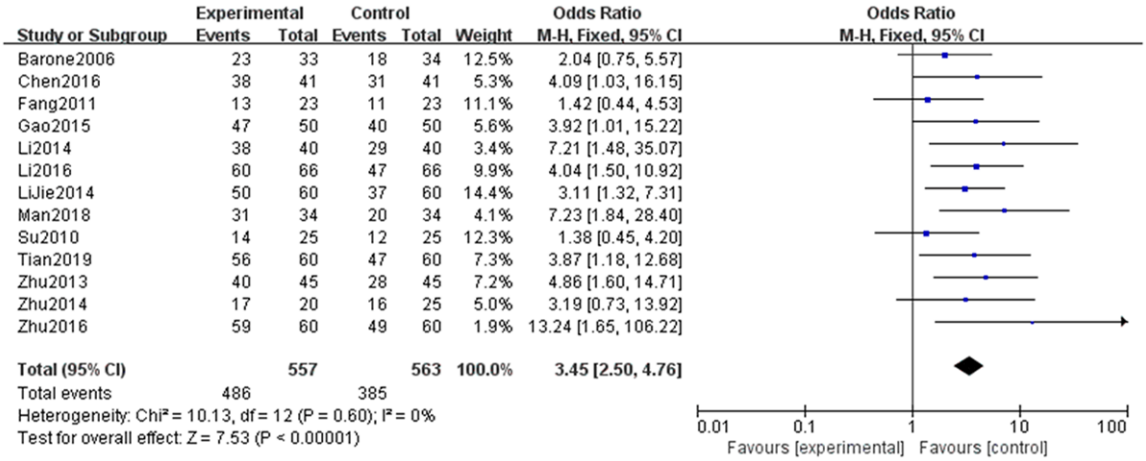

Figure 3. Efficacy of pramipexole in Parkinson's disease with anxiety or depression (fixed-effects model).

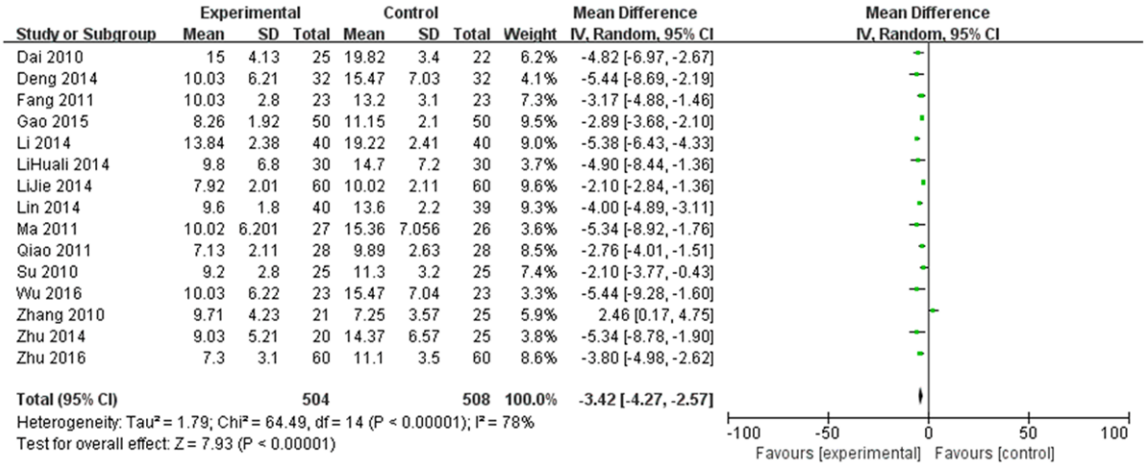

Figure 4. Effect of pramipexole on HAMD score in PD patients with depression.

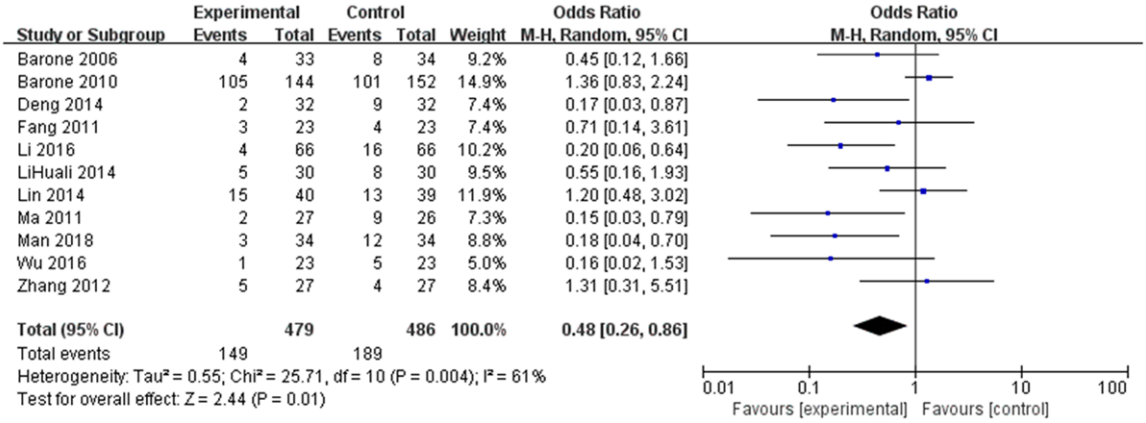

Figure 5. Forest plot of incidence of adverse events of pramipexole in the treatment of PD.

anism of pramipexole in Parkinson's disease with anxiety or depression.

Pramipexole is a non-ergot dopamine receptor agonist, which has selective affinity for dopa-

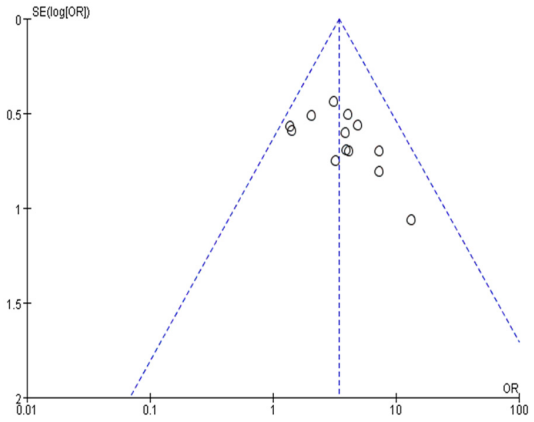

Figure 6. The funnel plots for effect.

mine D2 receptor family and high affinity for D3 receptor in this family [39]. Studies have shown that it can protect nerve cells from MPP induced apoptosis, inhibit and reduce the damage of quinone to substantia nigra cells, and then reduce the adverse reactions caused by long-term use of levodopa [40-43]. Pramipexole sustained-release tablets also have a good effect on depression and sleep disorders in non-motor symptoms of Parkinson's disease [44, 45]. Many studies have shown that the mechanism of depression may be related to the decrease of dopamine (DA), norepinephrine (NA), 5-hydroxytryptamine (5-HT) and frontal cerebral blood flow [46-49]. Barone et al. [16] showed that 80% of the improvement of depressive symptoms in PD patients came from the direct antidepressant effect of pramipexole. In addition to biochemical factors, PD caused by motor dysfunction, and the resulting decline in social function, adaptability and other psychological factors are also important factors causing depression. Therefore, the improvement of exercise symptoms will also promote the improvement of depression symptoms.

There are some limitations in this. Firstly, the limited (21) studies were conducted only in the eastern area, which may impact on clinical heterogeneity. Secondly, there may exist other confounding factors. Therefore, more clinical studies are necessary to assess the efficacy.

Conclusion

In conclusion, the research demonstrated that pramipexole may improve the treatment efficacy and HAMD score in Parkinson's disease with anxiety or depression. Due the limited number of included studies, more RCTs are needed to support afore mentioned conclusion.

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Disclosure of conflict of interest

None.

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