Research Article

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Clinical effects of piribedil in adjuvant treatment of Parkinson's Disease: A meta-analysis

Abstract: Objective. To evaluate the clinical effects of piribedil in adjuvant treatment of Parkinson's Disease (PD) by pooling previously openly published studies. Methods. The related electronic databases of Medline (1960~2017.5), Cochrane central register of controlled trials (CENTRAL), EMBASE (1980~2017.5) and Wanfang (1986~20175.5) were searched by two reviewers (Lu Peihua and Wang Jianqian) independently for publications including the topic of prospective randomized controlled trials about clinical effects of piribedil in adjuvant treatment of PD. The data of each included study was extracted and pooled by Stata11.0 software (for meta-analysis). The statistical heterogeneity across the studies was evaluated by I^2 test and the publication bias was calculated by begg's funnel plot and Egger's line regression test. Results. After searching the related electronic databases of Medline, CENTRAL, EMBSE and Wanfang databases, 11 clinical studies were included in this meta-analysis. The pooled RR (random effect model) of clinical efficacy was 1.29 (95%CI:1.18~1.41, P=4×10^{-3}) indicating the clinical efficacy of piribedil group was signficat higher than those of control group. The standard mean difference (SMD) for UPDRS score changed before and after treatment was pooled by random effect model. The combined SMD was -0.41 (95%CI:-0.75~-0.06). For piribedil related side effects, the combined data indicated that there was no statistical difference for nausea and vomiting (RR=0.43, 95%CI:0.41~1.69, P=0.61), mental disorders (RR=0.85, 95%CI:0.45~1.59, P=0.61) and other toxicities (RR=0.32, 95%CI:0.09~1.16, P=0.08). Conclusion. Piribedil combined with Levodopa in adjuvant treatment of PD is more effective than Levodopa alone without increasing the drug related toxicity.

Keywords: Parkinson's Disease; Meta-analysis; Clinical controlled trial; Adjuvant treatment; Piribedil; Levodopa

1 Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases seen in clinic [1]. The main clinical features of PD are a group of clinical syndromes characterized mainly by static tremor, muscular rigidity, movement retardation and postural instability. The main pathological characteristics of PD are selective neuronal degeneration of dopamine neurons in striatum and characteristic eosinophilic inclusion bodies presenting in the remaining neurons [2, 3]. Therefore, the enzymes involved in the synthesis and metabolism of dopamine may become a drug target for the treatment of PD.

Piribedil also known as Pronoran, Trivastal Retard, Trastal, Trivastan and Clarium, is an antiparkinsonian agent and piperazine derivative which acts as a D2 and D3 receptor agonist. It also has α2-adrenergic antagonist properties [4, 5]. Piribedil is a direct dopamine agonist, in clinical use for treatment of dopaminergic system dysfunction. Recent work suggests that it is selective for the D3 subtype, for which it has 20 times higher affinity than for D2, and possesses no significant affinity for D1 receptors. Piribedil was used in treatment of PD, either as monotherapy (without levodopa) or in combination with levodopa therapy, in the early stages of the disease as well as in the advanced stages. Several published studies have evaluated the clinical efficacy and toxicities of piribedil combined with levodopa vs levodopa alone in the treatment of PD [6, 7]. However, the sample size of each individual study was small and the statistical power is weak. Therefore, we performed this meta-analysis by pooling the openly published data about piribedil combined with levodopa versus levodopa alone in the treatment of PD to further evaluate its clinical efficacy and providing more evidence for clinical practices.

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2 Materials and methods

2.1 Publication searching

Prospective clinical studies about Piribedil combined with Levodopa vs Levodopa alone in the treatment of PD were electronicly searched in the electronic databases of Medline, the Cochrane central register of controlled trials (CENTRAL), EMBASE and Wanfang databases. The following search terms were used in searching each electronic database: "Parkinson's Disease", "PD", "paralysis agitans", "piribedil", "Pronoran", "Trivastal Retard", "Trastal", "Trivastan", "Clarium", "Levodopa"and "L-DOPA". Searches were limited to human trials, with the language restriction of English and Chinese. The publication searches were performed by two reviewers (Lu Peihua and Wang Jianqian) independently. The references of the related articles were also reviewed to find any potential suitable publications.

2.2 Publication inclusion and exclusion criteria

The publication inclusion criteria were made according to the study type, patients, treatment methods, treatment regimen of experiment and control groups and the outcomes of the original publications:(1) The study type was prospective randomized controlled trials; (2) The patients were clinically diagnosed with PD; (3) Patients in the piribedil group were treated with Piribedil combined with Levodopa; (4) Patients in the control group were treated with Levodopa alone; (5)For the outcome, the original study should provided the treatment clinical efficacy, Unified Parkinson's Disease Rating Scale (UPDRS) score changes and drug related toxicities. The title and abstract of the potential applicable studies were reviewed firstly to evaluate whether it was appropriate for inclusion criteria or not. Then all the potentially suitable studies were further evaluated as full-text papers.

2.3 Data extraction

Two reviewers (Lu Peihua and Wang Jianqian) independently reviewed the full-text papers and extracted the data from each of the included studies. The extracted data and information included: (1) Journal of the study published; (2) First and corresponding authors; (3) The paper publication year; (4) The country or area the study

was performed; (5) The treatment regimen; (6) The sample size; and (7) outcomes such as clinical efficacy, UPDRS score changes and drug related toxicities. The results were cross-checked.

2.4 Statistical analysis

STATA/SE 11.0 software（for meta-analysis version）was used for the statistical analysis. Dichotomous data such as clinical efficacy and drug related side effects was demonstrated by risk ratio (RR). The measurement data such as UPDRS score changes was expressed by mean with its standard difference. The statistical heterogeneity of the included 11 publications was evaluated by I^2 test [8]. The data were pooled by fixed or random effect model according to the statistical heterogeneity. The publication bias was assessed by Begg's funnel plot and Egger's line regression test. P<0.05 was deemed as statistically different [9].

3 Results

3.1 Publications searching

After searching the related electronic databases of Medline (1960~2017.5), CENTRAL, EMBASE (1980~2017.5) and CNKI (1986~20175.5), we firstly identified 369 relevant publications. After reading the titles and abstracts, 293 studies were excluded for not being suitable for inclusion. Seventy-six papers were reviewed as full text papers. Finally 11 clinical studies [6, 7, 10-18] were finally included in this meta-analysis. The publication inclusion process is shown in Figure 1. The general character of the included individual 11 publications are demonstrated in Table 1.

3.2 Clinical efficacy

Nine studies evaluated the clinical efficacy between piribedil and control groups. We firstly evaluated the statistical heterogeneity of the 9 included studies by I^2 test and found the statistical heterogeneity was not significant (I^2=44.9%, P=0.07). The clinical efficacy was pooled by fixed effects model. The pooled RR was 1.29 (95%CI:1.18~1.41, P=4×10^{-3}), Figure 2. This indicated that in patients with PD, treatment with piribedil combined with levodopa can significant improve the clinical efficacy.

Table 1: The general features of the included RCTs

First author	Country	Sample size	Age (year)	Regimen	Outcome	Course (moth)
Thobois2013	France	19	58.6±6.5	Piribedil 300gm/d+Levodopa 75-300mg/d	Efficacy, UPDRS, HAMD, Side effects	3
Ziegler2003	France	61	63.4±7.3	Piribedil 150gm/d+Levodopa 423 mg/d	Efficacy, UPDRS, Side effects	6
Tang GW2007	China	25	58.8±8.9	Piribedil 150gm/d+Levodopa 125 mg/d	Efficacy, UPDRS	3
Peng X2014	China	29	60.6±7.1	Piribedil 100-150gm/d+Levodopa 500-1000 mg/d	Efficacy, UPDRS, Side effects	6
Du DQ2013	China	21	Na	Piribedil 100-150gm/d+Levodopa 250-750 mg/d	Efficacy, Side effects	4
Mao KS2014	China	38	NA	Piribedil 150gm/d+Levodopa 125-1000 mg/d	Efficacy, UPDRS	4
Wang WF2010	China	36	NA	Piribedil 100gm/d+Levodopa 125-500 mg/d	UPDRS	6
Cheng YB2007	China	20	62.8±5.2	Piribedil 50-100gm/d+Levodopa 150 mg/d	UPDRS, HAMD	6
Zheng CM2010	China	29	64.3±7.1	Piribedil 150-250gm/d+Levodopa 300-600 mg/d	Efficacy, UPDRS	12
Qian JJ2007	China	15	63.5±6.0	Piribedil 50gm/d+Levodopa 250 mg/d	UPDRS	6
Gong XY2016	China	140	68.2±2.4	Piribedil 100-150gm/d+Levodopa 375mg/d	Efficacy, UPDRS	6

3.3 UPDRS score

Nine studies reported the UPDRS score before and after treatment. Significant statistical heterogeneity was foud in the effect size of standard mean difference (SMD) for UPDRS score changes(I^2=75.0%). The SMD was pooled by random effect model. The combined SMD was -0.41(95%CI:-0.75~-0.06), Figure 3. These results demonstrated that the UPDAR I score can be significantly improved in patients that receive combined treament.

3.4 Side effects

Five studies reported drug related nausea and vomiting side effects; 5 studies provided data on mental disorders of the two groups and 3 publications reported other side effects related to piribedil. There was no statistical heterogeneity for side effect evaluation parameters. The data was pooled by fixed effect model. The combined data indicated that there was no statistical difference for drug related side effects of nausea and vomiting (RR=0.43, 95%CI:0.41~1.69, P=0.61), mental disorders (RR=0.85, 95%CI:0.45~1.59, P=0.61) and other toxicities (RR=0.32, 95%CI:0.09~1.16, P=0.08), Figure 4. The pooled toxicity

indicated the combined treatment didn't elevate the drug related toxicity risk.

3.5 Publication bias evaluation

We used Begg's funnel plot and Egger's line regression test to assess the publication bias for each effect size. There were no significant publication biases for clinical efficacy (t=0.41, P=0.69), Figure 5; UPDRS score changes (t=0.06, P=0.97), Figure 6; and side effects (t=-1.18, P=0.53), Figure 7. All of the funnel plots showed approximately left and right symmetry.

4 Discussion

Although the clinical symptoms and characteristics of PD have been described in detail in the past two centuries, the exact etiology and pathogenesis remain incompletely understood [19, 20]. Previously published studies showed that the incidence of PD is associated with nigrostriatal degeneration and significant decrease of dopamine levels in the brain [21-23]. The main pathological changes of PD are selective neuronal degeneration of dopamine neurons in striatum and characteristic eosinophilic inclusion
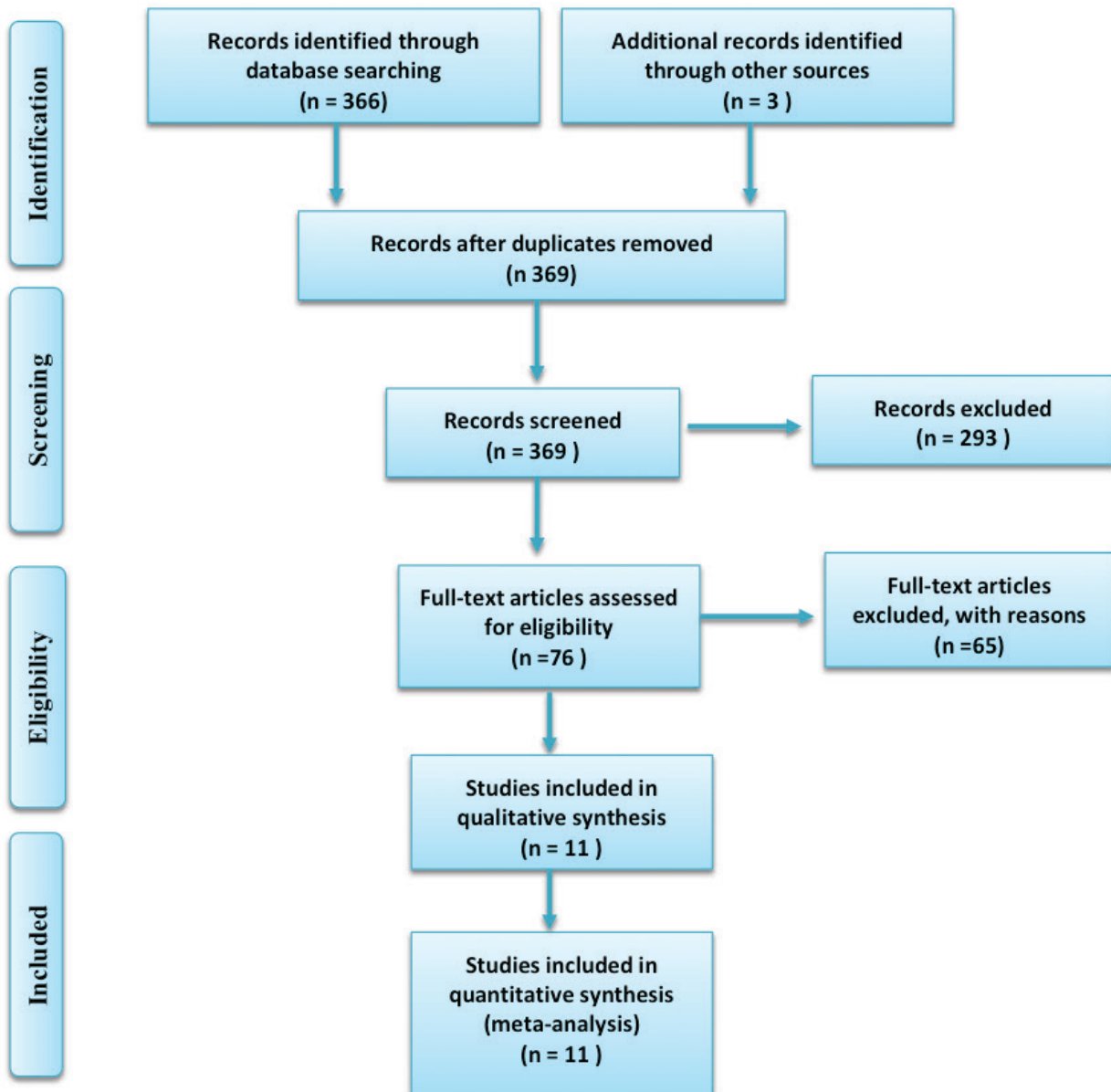
Figure 1: The searching flow chart of this meta-analysis

bodies present in the remaining neurons. At present, the most effective treatment for PD is levodopa combined with dopa decarboxylase inhibitors. However, long-term use of these drugs can lead to dyskinesia, "agent end effect" and "open - pass" phenomenon and other adverse reactions.

Piribedil is a synthetic non-ergot dopamine receptor agonist which selectively and directly stimulates the nigrostriatal pathway D1 and postsynaptic D2 receptor and limbic pathway D3 receptor. Previously studies indicated that Piribedil can increase dopamine receptor excitability, thereby improving motor symptoms in patients.

Clinical efficacy and drug related toxicity of Piribedil in adjuvant treatment of Parkinson's Disease had been widely discussed according to the previously pubished

studies. Zheng CM and his colleges [17] performed a prospective randomized clinical trial including 60 patients with PD and randomly divided them into control and experimental groups. Patients in the control group were given levodopa only and patients in the experimental group were administered levodopa and piribedil. After 12 months administration, the authors found that the clinical efficacy in the experimental group was significantly higher than those of control group and the UPDRS score was also significantly lower in the experimental group than that of control group after treatment. However, the improved clinical efficacy and UPDRS score were not found in another clinical trial performed by Du DQ and et al [13]. So, the clinical efficacy of Piribedil in adjuvant
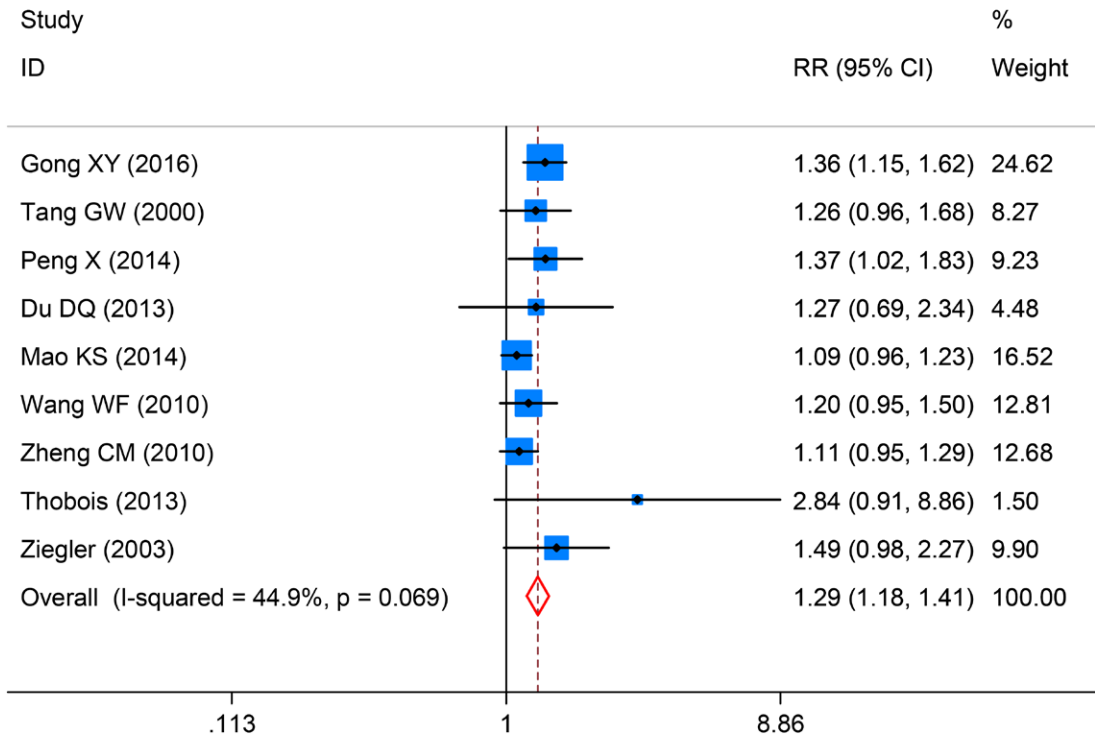
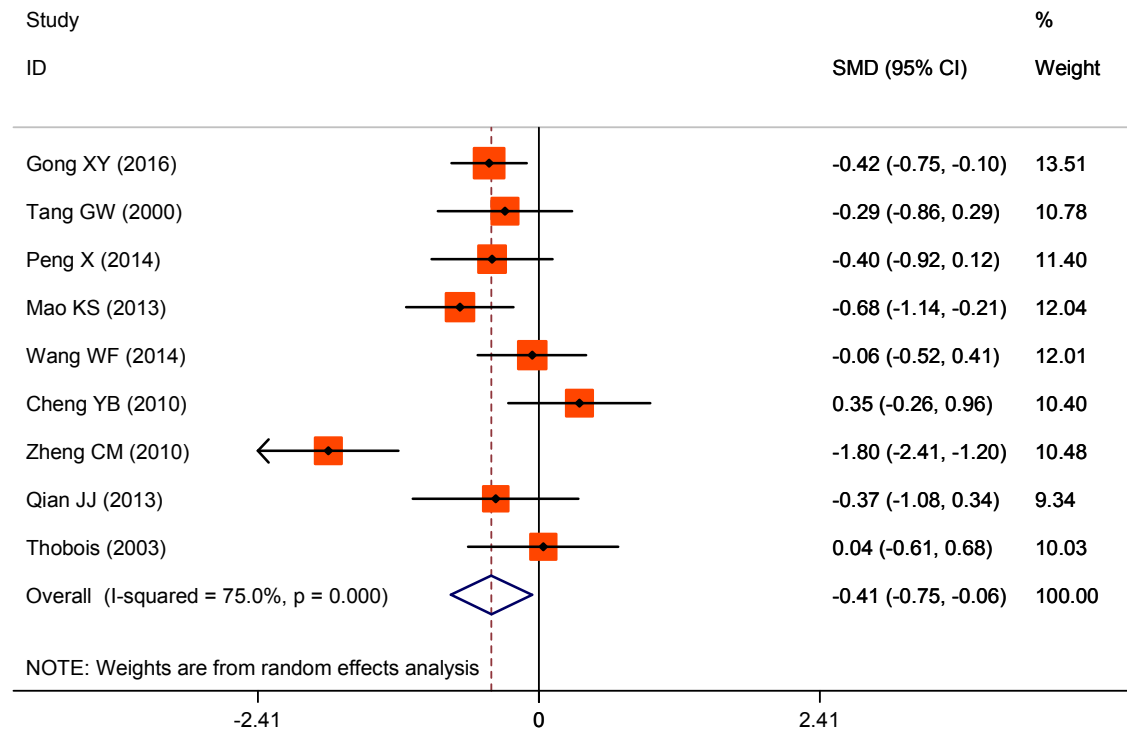**Figure 2:** Forrest plot of clinical efficacy for piribedil in adjuvant treatment of Parkinson's Disease

Figure 3: Forrest plot of UPDRS score changes for piribedil in adjuvant treatment of Parkinson's Disease
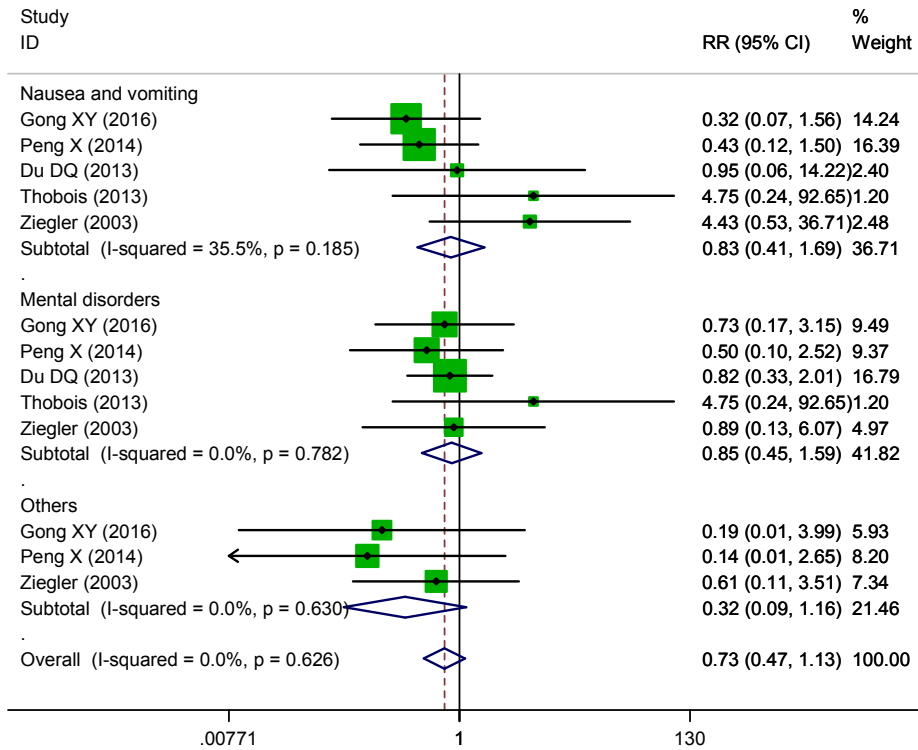
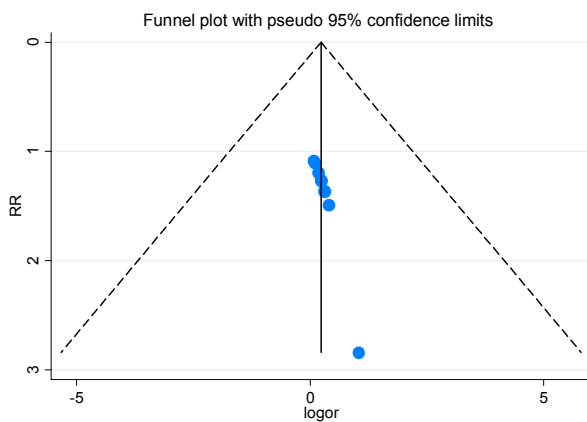**Figure 4:** Forrest plot of side effects of piribedil in adjuvant treatment of Parkinson's Disease

Figure 5: The Begg's funnel plot for clinical efficacy of piribedil in adjuvant treatment of Parkinson's Disease
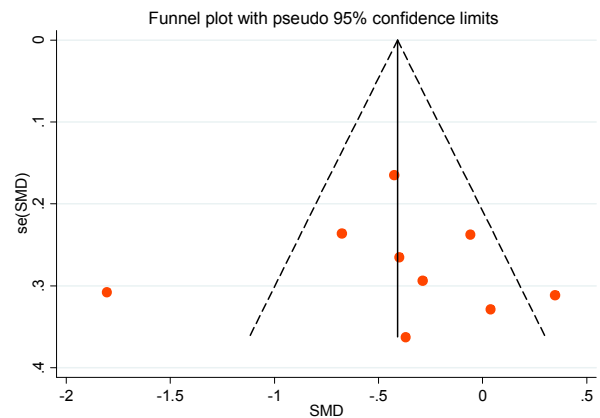

Figure 6: The Begg's funnel plot for UPDRS score changes of piribedil in adjuvant treatment of Parkinson's Disease

treatment of PD was not consistent. This may be due to the small sample size of each individual study with limited statistical power. Therefore, high quality meta-analysis was needed to further quantify the clinical efficacy of Piribedil in adjuvant treatment of PD by pooling data from previously openly published studies, which can increase the statistical power and provide more information for its clinical usage.

In our present meta-analysis, we systematically searched the electronic databases and finally included 11 clinical trials and evaluated the pooled clinical efficacy,

UPDRS score changes and drug related toxicities. The pooled results indicated the clinical efficacy of piribedil group was signficantly higher than those of the control group (P<0.05). Clincial efficacy of patients with PD can be significantly improved by adding the piribedil. These results were in accordance with most of the previously published studies [4,8]. We also found that the combined treatment can signifcantly decrease the UPDRS I score compared to the control group. This indicated that the symptoms can be improved by adding piribedil. However, the combined treatment did not increase drug related
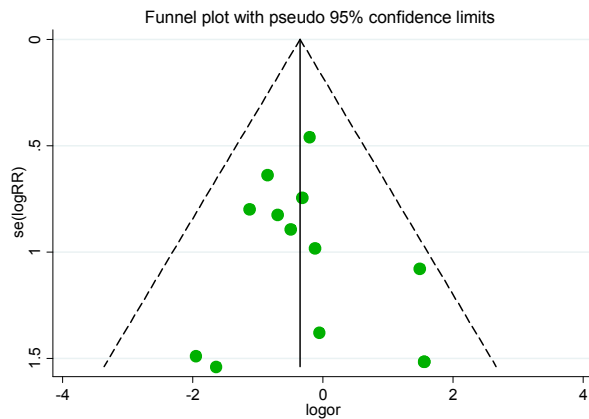
Figure 7: The Begg's funnel plot for side effects of piribedil in adjuvant treatment of Parkinson's Disease

toxicities such as gastrointestinal reaction, mental disorders and other side effects. This meta-analysis indicated piribedil combined with levodopa in adjuvant treatment of PD is more effective than levodopa alone without increasing the drug related toxicity.

Our work found that piribedil combined with levodopa can significantly improve the clinical efficacy and UPDRS score in treatment of PD. However, there are two limitations for this meta-analysis. Firsly, we only inlcuded studies published in Chinese and English. Secondly, the treatment course of each individual study was not in accordance with the others; this may be a important clincial heterogeneity. In view of the above limitations, multi-center prospective randomized controlled trials with large samples are needed for further evaluation of the clinical efficacy of piribedil in adjuvant treatment of PD and provide more confident conclusions for clinical practices.

Conflict of interest statement: Authors state no conflict of interest.

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