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Comparative Analysis of the Effects of Escitalopram, Pramipexole, and Transcranial Magnetic Stimulation on Depression in Patients With Parkinson Disease: An Open-Label Randomized Controlled Trial

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Objective: This study aimed to compare the effects of different antidepressant therapies on depression in patients with Parkinson disease (PD) and to provide a reference for clinical treatment.

Methods: A total of 328 patients with idiopathic PD were selected consecutively. Subjects met *Diagnostic and Statistical Manual of Mental Disease*, *Fourth Edition*, criteria for a depressive disorder, or operationally defined subsyndromal depression, and scored greater than 17 on the 17-item Hamilton Depression Scale (HAMD-17). One hundred thirty-one patients with PD accompanied with depression were enrolled into the experimental group. The subjects were randomly divided into 4 groups, and 118 were eventually completed: routine treatment group (n = 29), routine treatment + escitalopram group (n = 29), routine treatment + pramipexole group (n = 31), and routine treatment + transcranial magnetic stimulation (TMS) group (n = 29). After 4 weeks of treatments, the efficacy of each treatment was evaluated using HAMD score and reduction rate.

Results: After 4 weeks of treatment, the HAMD score was used for pair-to-pair comparison between the 4 groups. The therapeutic efficiency of escitalopram, pramipexole, and repetitive TMS was superior to routine anti-PD treatment, and the differences were statistically significant ($P < 0.05$). There was no statistical difference between escitalopram and pramipexole, but all of them were superior to rTMS. Further logistic regression analysis suggested that 50% reduction in HAMD score from baseline was associated with the treatment method. Among them, escitalopram had statistical significance ($P < 0.05$).

Conclusions: Escitalopram, pramipexole, and high-frequency TMS had better efficacy in patients with PD complicated with depression. At 4 weeks, escitalopram showed better antidepressant effects and improved patients' quality of life and did not worsen motor function.

Key Words: depression, HAMD, Parkinson disease, therapy

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BACKGROUND

Parkinson disease (PD) is considered to be the second most prevalent neurodegenerative disease only after Alzheimer disease. As its prevalence increases with age, PD is one of the most common age-related brain diseases.[1] Recent studies of PD have increasingly focused on the nonmotor symptoms of PD, including depression, anxiety, sleep disorders, and cognitive dysfunction,[2] with depression in PD (dPD) being the most common in patients with PD.[3,4] Numerous studies have demonstrated that compared with motor symptoms, nonmotor symptoms, especially depression and cognitive dysfunction, have greater effects on the quality of life of patients with PD.[5] Therefore, early diagnosis and treatment of such symptoms would play an essential role in improving the quality of life of the patients and reducing the burdens of their families and the society.

At present, the prevalence of dPD oscillates between 40% and 50%,[6] while less than 20% of the patients have received any antidepressant therapy. Untreated dPD can severely affect the quality of life of patients and increase the risk of suicide.[7] Manifestations of dPD include low mood, emotional indifference, easy fatigue, sleep disorder, etc. Daily living ability and cognitive function may also be affected.[8,9] However, the diagnosis of dPD is still difficult at present, mainly because the symptoms of depression and PD are overlapped and similar, and it is not easy to detect depression at the early stage.[10,11] Besides, in clinical practice, both patients and clinicians pay more attention to the improvement of motor symptoms during treatment but ignore the changes in psychological state or simply do not distinguish depressive symptoms from PD conditions. In addition, the nature of PD as an incurable progressive disease, as well as the behavioral and emotional effects of pharmacological treatment against PD, can complicate the assessment of depressive symptoms.[12] Currently, no particular diagnostic criteria have been published for dPD; patients who satisfy both the criteria of idiopathic PD published by the UK Parkinson's Disease Association Brainpools and the criteria of major depression listed in *Diagnostic and Statistical Manual of Mental Disease*, *Fourth Edition*,[13] are considered to be subjects of dPD.

Most of the current drugs prescribed for dPD are general antidepressants, such as selective serotonin reuptake inhibitors, 5-5 Hydroxyl Tryptamine (5-HT) selective norepinephrine reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitor antidepressants.[14] Several nonpharmaceutical treatments have emerged in clinical practice in recent years, including cognitive

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This study was reviewed and approved by the ethics committee of the Affiliated Hospital of Guizhou Medical University, and all subjects voluntarily signed the informed consent.

Written informed consent to publish this information was obtained from study participants.

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

J.C. designed experiments, wrote papers, and obtained research funds. P.F.X. did the implementation of research, data collection, and data analysis. X.Y.G. did the statistical analysis. T.Z. did the research guidance, technical support, and paper revision. All authors have read and approved the manuscript.

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therapy,[15] electroconvulsive therapy,[16] transcranial magnetic stimulation (TMS),[17] and other psychological and physical therapies, but the efficacy of each therapy remains unclear.[18] Overall, treatment options for patients suffering from dPD are still limited. Therefore, the development and validation of new therapies have become a priority.[19]

The purposes of this study were to compare the effects of escitalopram, pramipexole, and repetitive transcranial magnetic stimulation (rTMS) on depression in patients with PD, to explore the effective treatment methods for PD with depression, and to provide suggestions for clinical selection of medication and treatment methods.

METHODS

Subjects

Three hundred twenty-eight patients with idiopathic PD admitted to the Neurology Department and Ward of the Affiliated Hospital of Guizhou Medical University and Second People's Hospital of Guiyang were consecutively assessed for eligibility of the study. An onsite survey was conducted for the patients to collect demographic information and medical history. To be included, the subject must: (1) meet the diagnostic criteria of United Kingdom Parkinson's Disease Society Brain Bank; (2) meet the diagnostic criteria for at least one *Diagnostic and Statistical Manual of Mental Disease*, *Fourth Edition*,–listed depressive disorder[20] (ie, major depressive disorder, dysthymic disorder, minor depressive disorder) or operationally defined subsyndromal depression; (3) have a score greater than 17 on Hamilton Depression Scale (HAMD-17); (4) be at stages 2 to 4 on the Hoehn-Yahr (H-Y) scale; and (5) have no communication disorders and be able to complete the questionnaires independently. Patients were excluded if they met one or more of the exclusion criteria as follows: (1) PD was caused by cerebrovascular diseases, central nervous system infection and poisoning, and/or craniocerebral trauma; (2) the patient had Parkinson-plus syndromes, such as multiple-system atrophy, progressive supranuclear palsy, corticobasal degeneration, and dementia with Lewy bodies; (3) the patient experienced severe cognitive dysfunction or mental disorders; and (4) the patient had received any antidepressants in the past 3 months. All eligible subjects voluntarily participated in the study and provided written informed consent.

CLINICAL MEASUREMENTS

The Unified Parkinson's Disease Rating Scale (UPDRS) is the most commonly used rating scale and the criterion standard for the assessment of PD symptoms.[21] The UPDRS contains 4 subscales to measure (1) behavior and mood, (2) self-reported daily activities (eg, swallowing, speech, handwriting), (3) motor function, and (4) any complication of the therapy. Each of the 42 item is scored on a 5-point scale (0 = "normal"; 4 = "severe").

The severity of PD was graded according to Hoehn-Yahr Staging Scale.[22] This scale classifies the progression of PD into 5 stages according to the severity of impairment and disability relevant to the disease, with stage 1 being minimal or no functional disability and stage 5 being confinement to bed or wheelchair unless aided.

The 17-item other-rated HAMD was used to quantify each patient's severity of depression. The standard for evaluation is as follows: ≤7, not depressed; 8–17, depressed; 17–24, mild to moderate depressive symptom; and ≥24, severe depression.[23]

The Patient Health Questionnaire for self-administered measurement (PHQ-9) was used to assess depression within 2 weeks.[24] The 39-item Parkinson Disease Questionnaire (PDQ-39) was used to evaluate the quality of life of PD patients.[25]

ASSESSMENT AND RANDOMIZATION

Estimation of Sample Size

Referring to previous research experiments, the test efficiency ($1-\beta$) of this experiment was set as 80%, and the test level (α) was set as 0.05. The difference test of the mean comparison between the 2 groups was used to estimate the sample content: the average difference between the treatment group and the control group was 4.2, and the difference of standard deviation was 1.1, the sample content was calculated to be 27. For the convenience of statistics, we take the sample size of each group as 30.

Grouping and Treatment Methods

Patients who met the inclusion criteria continued conventional anti-PD therapy (including dopamine [DA] agents, anticholinergic drugs, etc) and underwent different antidepressant therapy. Using random grouping, software was used to generate random number for each patient participating in the clinical trial. The subjects were randomly divided into 4 groups: routine treatment group, routine treatment + escitalopram group, routine treatment + pramipexole group, and routine treatment + TMS group. In each group of 30 people, clinical control was performed after 4 weeks of treatment.

Before the treatment, the participants were first evaluated at a screening visit, during which informed consent was obtained, and eligibility criteria and demographic information were verified. Initially, a total of 131 patients were included in the study, and the subjects were randomly divided into 4 groups: routine treatment group (n = 33), in which patients were treated with routine anti-PD drugs (mainly: levodopa and benserazide tablets, dose: 0.25–1 g/d, combined use of other anti-PD drugs; no intervention was made according to the patient's routine dose). Routine treatment + escitalopram group (n = 31), in which patients were treated with routine anti-PD drugs + escitalopram oxalate. The investigator then adjusted the dosage of the experimental medications as necessary and tolerated, up to a maximum daily dosage of 10 mg. Routine treatment + pramipexole group (n = 34), with an initial dose of 0.375 mg/d in week 1; if the PD patients could tolerate, the dose was increased to 0.75 mg/d in week 2 and 1.5 mg/d in week 3. Routine treatment + high-frequency rTMS group. High-frequency 5 Hz stimulated the left dorsolateral prefrontal region once a day for 20 minutes at a time, 5 times per week (n = 33).

A total of 13 subjects stopped the experiment the experiment because of economic, traffic, and compliance problems. Four patients were lost in routine group, 2 in escitalopram group, 3 in pramipexole group, and 4 in rTMS group. Eventually, 118 people (routine treatment = 29, escitalopram group = 29, pramipexole group = 31, and rTMS group = 29) completed the study.

Outcome Measures

The primary outcome measure was the change from baseline to week 4 in the 17-item HAMD, which was administered by the site investigator. The protocol specified that all evaluations should be conducted in the "on" state for patients who experienced motor fluctuations, the "on" state refers to the normal activity and disappearance of limb stiffness in patients without any relevant treatment.

The secondary outcome measures for antidepressant efficacy was changes in PHQ for self-administered measurement (PHQ-9) at week 4. Prespecified dichotomous HAMD outcomes were assessed, including HAMD ≤ 7 at week 4 ("remission") and a ≥ 50% reduction in HAMD score from baseline to week 4 ("response").

Other outcome measures included the UPDRS total and the PDQ-39 to assess PD motor function as well as measures of quality of life.

TABLE 1. Sociodemographics and Clinical Characteristics of the Patients With dPD

Variable	Routine Group (n = 29)	Escitalopram (n = 29)	Pramipexole (n = 31)	rTMS (n = 29)	F/χ^2	*P*
Sex						
Male	11 (37.9%)	12 (41.4%)	12 (38.7%)	12 (41.4%)	0.118	0.99
Female	18 (62.1%)	17 (58.6%)	19 (61.3)	17 (58.6%)		
Age	63.7 ± 8.88	64.34 ± 9.68	64.35 ± 8.93	64.17 ± 8.37	0.158	0.925
Course of disease	3.79 ± 3.07	3.59 ± 3.70	3.71 ± 2.47	4.14 ± 2.47	0.226	0.878
Education	7.13 ± 3.51	6.72 ± 2.87	6.25 ± 3.27	7.02 ± 3.10	0.421	0.732
HAMD	23.38 ± 4.72	23.93 ± 4.40	23.90 ± 3.97	22.48 ± 4.19	0.719	0.543
PHQ-9	16.86 ± 2.92	17.45 ± 2.81	16.74 ± 2.11	17.24 ± 2.08	0.509	0.677
PDQ-39	60.21 ± 8.37	59.72 ± 11.06	57.42 ± 9.30	58.57 ± 15.32	0.597	0.618
UPDRS-III	23.23 ± 6.38	23.41 ± 7.73	23.13 ± 6.81	22.52 ± 5.79	1.127	0.341
H-Y	0.341	2.82 ± 0.57	2.73 ± 0.66	2.64 ± 0.68	1.105	0.35

Statistical Methods

The Epidata 3.1 software was used for double entry and error detection, and the SPSS 25.0 software was used for data analysis and statistics. Descriptive statistics were generated for all variables. Independent sample *t* test (for continuous variables) and χ^2 test (for categorical variables) were used to on different sociodemographic variables. The comparison of paired data was performed by paired *t* test, and the difference among different groups was conducted by 1-way analysis of variance. The follow-up period was 4 weeks. Covariance analysis was used to compare the HAMD score among the different treatment groups and adjust the difference of baseline score. For categorical outcome variables at week 4 (HAMD ≤ 7 and ≥ 50% reduction in HAM-D score from baseline), a logistic regression model that included treatment group, age, course of disease, sex, and baseline HAM-D score as independent variables was used to estimate the odds ratios comparing each active treatment group with the routine treatment group. Ninety-five percent confidence intervals (CIs) were calculated for the changes in score. All tests were 2-sided with a *P* value equal to 0.05.

Results

Table 1 compares the sociodemographics and clinical characteristics of patients with dPD. The 1-way analysis of variance and χ^2 test revealed no significant differences in sex, age, course of disease, education level, HAMD score, PHQ-9 score, PDQ-39 score, UPDRS-III score, and H-Y staging among the 4 groups. The results of the analysis showed that the study grouping was reasonable.

One-way analysis of variance was adopted for multiple comparison of the results of HAMD, PHQ-9, UPDRS-III, and PDQ-39 of the 4 groups at week 4 of treatment. The pairwise comparisons were conducted using the least significant difference method. The results showed that escitalopram (5.62; 95% CI, 3.46 to 7.78; $P < 0$), pramipexole (4.37; 95% CI, 2.24 to 6.49; $P < 0$), rTMS (3.21; 95% CI, 1.05 to 5.37; $P < 0$), relative to routine group were statistically significant in HAMD scores. The mean response did not differ significantly between the escitalopram and pramipexole groups ($P = 0.24$). Escitalopram (−2.41; 95% CI, −4.58 to 0.25; $P = 0.029$), relative to rTMS, was statistically significant. Escitalopram (2.90; 95% CI, 1.41 to 4.39; $P < 0$), pramipexole (2.77; 95% CI, 1.30 to 4.24; $P < 0$), and rTMS (2.35; 95% CI, 0.85 to 3.84; $P = 0.002$), relative to routine group, were statistically significant in PHQ-9 scores. Escitalopram (6.96; 95% CI, 1.10 to 12.83; $P = 0.20$) and pramipexole (7.69; 95% CI, 1.92 to 13.45; $P = 0.009$), relative to routine group, were statistically significant in PDQ-39 scores. Pramipexole (2.37; 95% CI, 0.87 to 3.95; $P = 0.028$) and rTMS (1.98; 95% CI, 0.73 to 3.89; $P = 0.036$), relative to escitalopram, were statistically significant

TABLE 2. Treatment Effects on Primary and Secondary Outcome Variables at Week 4

Variable	Routine ① (n = 29)	Escitalopram ② (n = 29)	Pramipexole ③ (n = 31)	rTMS ④ (n = 29)	*F*	*P*	Pairwise Comparison *P* < 0.05
HAMD	19.14 ± 4.80	13.52 ± 4.69	14.77 ± 2.12	15.93 ± 4.50	9.795	0.001*	① > ② ① > ③ ① > ④ ④ > ②
PHQ-9	14.93 ± 2.77	12.03 ± 3.42	12.16 ± 1.93	12.59 ± 3.15	6.54	0.001*	① > ② ① > ③ ① > ④
UPDRS-III	20.52 ± 6.23	21.58 ± 6.10	19.21 ± 6.76	19.60 ± 5.89	5.84	0.039†	② > ③ ② > ④
PDQ-39	53.62 ± 9.87	46.66 ± 13.14	46.71 ± 9.74	49.26 ± 13.03	2.8	0.043†	① > ② ① > ③
Analysis of covariance							
HAMD	19.14 ± 4.80	13.52 ± 4.69	14.77 ± 2.12	15.93 ± 4.50	25.27	<0.001*	① > ② ① > ③ ① > ④ ④ > ② ④ > ③

*$P < 0.01$.

‡$P < 0.05$.

in UPDRS-III scores. Furthermore, analysis of covariance was used to compare HAMD scores among 4 groups. Escitalopram (6.62 ± 0.74, t = 8.10, P < 0.001), pramipexole (4.37 ± 0.73, t = 6.48, P < 0.001), and rTMS (3.21 ± 0.74, t = 3.46, P = 0.001), relative to routine group, were statistically significant in HAMD scores. Escitalopram (2.41 ± 0.75, t = −4.60, P < 0.001) and pramipexole (−1.16 ± 0.73, t = −2.94, P = 0.004), relative to rTMS, were statistically significant. The mean response did not differ significantly between the escitalopram and pramipexole groups (P = 0.083). Details are available in Table 2.

A logistic regression model was used to assess and compare the dominance ratios of the 4 groups, using HAMD score of 7 or less and HAMD reduction rate greater than 50% or less as dependent variables, and basic personal characteristics and grouping as independent variables, respectively. The HAMD score of 7 or less was used as the dependent variable and sex, age, course of disease, years of education, and grouping were used as independent variables, and the results showed no statistical significance (P > 0.05; Table 3). The HAMD reduction rate of 50% or greater (50% reduction in HA M-D score from baseline) as the dependent variable, sex, course of disease, years of education, and baseline HAMD score as independent variables, no statistically significant has been found (P > 0.05), but age and different treatment groups were statistically significant and entered the regression model. The 2 cases indicates that different treatment regimens were independent influences on the rate of HAMD score reduction after 4 weeks of treatment (escitalopram group, with an odds ratio of 14.737 [95% CI, 1.74–124.82; df = 1; P = 0.014], age, with an odds ratio of 0.932 [95% CI, 0.878–0.990; df = 1; P = 0.022]).

DISCUSSION

Depression is more common in patients with PD than in the normal elderly population and those with other chronic and disabling diseases.[26] In this study, moderate and severe patients with HAMD score greater than 17 were enrolled, considering that patients with mild depressive symptoms could relieve by self-adjustment after routine anti-PD treatment, as well as explanation and consolation from doctors, without the need for other antidepressant intervention.

After 4 weeks of dPD treatment, the results of our study showed that the therapeutic efficacy of escitalopram, pramipexol, and TMS was better than that of routine anti-PD therapy. There was a statistically significant antidepressant effect at 4 weeks of treatment as routine group + escitalopram versus pramipexol versus rTMS (P < 0.05). There was a statistically significant antidepressant response rate at 4 weeks of treatment as routine group + escitalopram versus pramipexol versus rTMS (P < 0.05). In addition, there was also a statistically significant antidepressant remission rate at 4 weeks of treatment as routine group + escitalopram versus pramipexol versus rTMS (P < 0.05). Escitalopram and pramipexol had no difference in effect but are superior to rTMS. These results are consistent with the previous studies. Current studies have found that abnormalities in neurotransmitters such as DA, serotonin (5-HT), and norepinephrine all play an important role in PD depression.[27,28] Pramipexol is a DA receptor agonist, whose target is not limited to the substantia nigra striatum region; meanwhile, it selectively acts on D_2 and D_3 receptors in hippocampus, amygdala, and other regions, and its affinity to D_3 receptors is significantly higher than D_2 receptors.[29] Consistent with previous results,[30,31] the current findings also indicate that pramipexol not only has a good therapeutic effect on PD-related motor symptoms but also can improve the depressive symptoms of patients. Therefore, it may be a potential antidepressant drug[32] for patients with dPD.

Escitalopram is a selective 5-HT reuptake inhibitor that inhibits the reuptake process by blocking the 5-HT reuptake pathway, thereby increasing the 5-HT concentration in the synaptic gap. It continuously stimulates the postsynaptic membrane, and finally, the antidepressant effect could be achieved.[33] This study found that escitalopram showed a more obvious effect after 4 weeks of treatment. Nevertheless, the logistic regression analysis revealed that the 4 groups did not differ significantly in efficacy if the treatment outcome was set as a HAMD score of 7 or less, which may be attributed to the short treatment time. Meanwhile, when using the HAMD score reduction rate of 50% or greater as the outcome index, there were differences between pramipexol and rTMS, suggesting that different treatments had independent effects on relieving depression. A recent study reported escitalopram (10–20 mg/d) was effective and well tolerated in Chinese patients with depression, which can improve 67.1% and 83.6% of clinical depressive symptoms at weeks 4 and 8, respectively.[34] Rohit and Kuljeet[35] reported that escitalopram may be a viable approach for the treatment of dPD. Our study found that escitalopram showed excellent antidepressant effects and improved quality of life at week 4 and had no effect on patients' motor function.

Our study found that escitalopram showed excellent antidepressant effects, improved quality of life at week 4, and had no effect on patients' motor function. High-frequency rTMS effectively improved depressive symptoms and dyskinesia in patients with dPD. However, the antidepressant effect of high-frequency rTMS was not as good as that of escitalopram and pramipexol. Previous studies showed that both high- and low-frequency rTMS have antidepressant effects but high-frequency rTMS is more effective.[36] A study found that high-frequency rTMS could also improve dyskinesia in patients with PD and facilitate recovery of motor function. The reason for rTMS to treat depression may be that it can cause changes in multiple neurotransmitters such as DA, 5-HT, glutamate, brain-derived neurotrophic factor, and so on.[37,38]

There are several limitations of this study. First, the conclusion may not reflect the long-term treatment effect as the treatment only lasted 4 weeks without follow-up. It is possible that treatment of depression in the context of PD may require higher doses and longer duration of antidepressants. Second, we did not take other combined anti-Parkinson drugs that might have had an effect on mood into consideration, which may confound the results. Third, most subjects had moderate depression, which may lead to selection bias modulating the findings. Fourth, one additional limitation was that because of the open-label design and lack of placebo, all the participants knew they were receiving some type of

TABLE 3. Logistic Regression for HAMD Score Reduction Rate on Depression in Patients With PD

		Odds Ratio	95% CI		
Variate	***B***		**Lower**	**Upper**	***P***
Sex	0.18	1.197	0.401	3.573	0.747
Age	−0.070	0.932	0.878	0.990	0.022
Course of disease	0.039	1.04	0.832	1.299	0.732
Baseline HAMD score	−0.457	0.633	0.096	4.18	0.635
Group					0.029*
Escitalopram	2.690	14.737	1.740	124.82	0.014*
Pramipexole	1.905	6.720	0.756	59.722	0.087
rTMS	1.500	4.48	0.469	42.791	0.193
Constant	0.427	1.498			0.854

*P < 0.05.

potential active antidepressant treatment. Finally, our sample size was not large enough to identify subject characteristics that can predict the response to medications.

CONCLUSIONS

Escitalopram, pramipexole, and high-frequency TMS had better efficacy in patients with PD complicated with depression. Escitalopram showed better antidepressant effects and improved patients' quality of life and did not worsen motor function. Although high-frequency rTMS was inferior to the previously mentioned 2 drugs in terms of therapeutic effects, it might be a good auxiliary treatment as a painless and noninvasive therapeutic method. These results should be confirmed in larger, controlled trials.

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