

Zishenpingchan granules for the treatment of Parkinson's disease: a randomized, double-blind, placebo-controlled clinical trial

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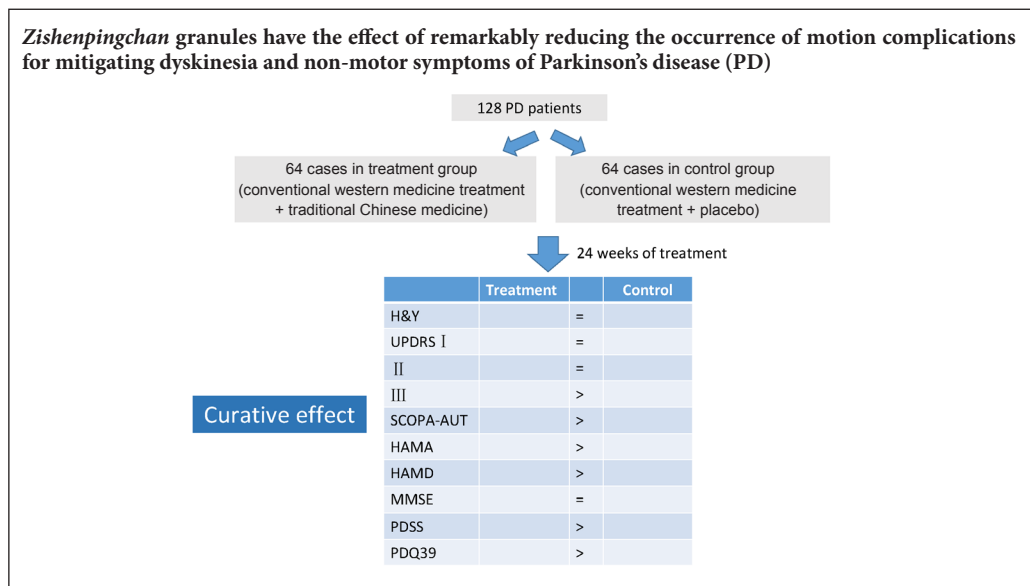
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Funding: This work was supported by a grant from Major Project of Shanghai Committee of Science and Technology of China, No. 15401970100; a grant from the National Natural Science Foundation of China (General Program), No. 81673726; a grant from the Project of Shanghai Committee of Science and Technology of China, No. 17401934600; a grant from Longhua Scholar Plan of National Traditional Chinese Medicine Clinical Base of China, No. LYTD-34; a grant from Shanghai Traditional Chinese Medicine Science and Technology Innovation Project, No. ZYKC201601002.

Graphical Abstract



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doi: 10.4103/1673-5374.235075

Accepted: 2018-03-07

Abstract

Levodopa preparations remain the preferred drug for Parkinson's disease. However, long-term use of levodopa may lead to a series of motor complications. Previous studies have shown that the combination of levodopa and *Zishenpingchan* granules (consisting of *Radix Rehmanniae preparata*, *Lycium barbarum*, *Herba Taxilli*, *Rhizoma Gastrodiae*, *Stiff Silkorm*, *Curcuma phaeocaulis*, *Radix Paeoniae Alba*, *Rhizoma Arisaematis*, *Scorpio* and *Centipede*) can markedly improve dyskinesia and delay the progression of Parkinson's disease, with especially dramatic improvements of non-motor symptoms. However, the efficacy of this combination has not been confirmed by randomized controlled trials. The current study was approved by the Hospital Ethics Committee and was registered in the Chinese Clinical Trial Register (registration number: ChiCTR-INR-1701194). From December 2014 to December 2016, 128 patients (72 males and 56 females, mean age of 65.78 ± 6.34 years) with Parkinson's disease were recruited from the Department of Neurology of Longhua Hospital and Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine in China. Patients were equally allocated into treatment and control groups. In addition to treatment with dopamine, patients in treatment and control groups were given *Zishenpingchan* granules or placebo, respectively, for 24 weeks. Therapeutic efficacy was assessed using the Unified Parkinson's Disease Rating Scale, on-off phenomenon, Hoehn-Yahr grade, Scales for Outcomes in Parkinson's disease–Autonomic, Parkinson's disease sleep scale, Hamilton Anxiety Scale, Hamilton Depression Scale, Mini-Mental State Examination, and the Parkinson's Disease Quality of Life Questionnaire. Artificial neural networks were used to determine weights at which to scale these parameters. Our results demonstrated that *Zishenpingchan* granules significantly reduced the occurrence of motor complications, and were useful for mitigating dyskinesia and non-motor symptoms of Parkinson's disease. This combination of Chinese and Western medicine has the potential to reduce levodopa dosages, and no obvious side effects were found. These findings indicate that *Zishenpingchan* granules can mitigate symptoms of Parkinson's disease, reduce toxic side effects of dopaminergic agents, and exert synergistic and detoxifying effects.

Key Words: nerve regeneration; levodopa; motion complications; non-motor symptoms; traditional Chinese medicine treatment; artificial neural networks; *Zishenpingchan* granules; randomized controlled trials; neurodegenerative diseases; neural regeneration

Introduction

Parkinson's disease (PD) is a central nervous system disorder associated with dyskinesia that occurs in middle-aged and elderly individuals. At present, there are more than 2 million PD patients in China, where it is estimated that the incidence of PD will rise to 4.94 million by 2030, ranking first in the world (Dorsey et al., 2007; Oosterveld et al., 2015). Although levodopa preparations remain the preferred drug for PD, with prolonged time of levodopa treatment, more than half of patients will suffer from a series of motor complications (Xing et al., 2014; Gibbins et al., 2017; Madan et al., 2017) that seriously affect the patient's daily life. In recent years, research has focused on the non-motor symptoms of PD, but current Western medicine treatments for non-motor symptoms are not good enough. Therefore, to develop an optimal drug treatment program that prevents and controls both motor complications and non-motor symptoms, researchers have explored Chinese medicine to provide significant improvements to the quality of PD patients' lives.

The deceased professor Jian-hua Hu, famous for Traditional Chinese Medicine in Shanghai, prescribed *Zishenpingchan* to treat PD after decades of repeated clinical exploration and verification based on Traditional Chinese Medicine theory, as well as references to folk prescription and Chinese medicine literature. It is an effective PD treatment, and has a China invention patent license (patent No. ZL201210210891.4) after decades of clinical application. In early clinical research, a combination of *Zishenpingchan* granules and levodopa was shown to significantly improve PD patients' dyskinesia and delay disease progression (Yuan et al., 2010; Zhou et al., 2014). Simultaneously, it has also been shown to be effective for improving the non-motor symptoms of PD (Gu et al., 2011), including improved quality of sleep, reduced autonomic nervous system dysfunction, relief of depression, and other effective improvements in the quality of PD patients' lives (Ye et al., 2014a). Thus, this study sought to evaluate the clinical efficacy and safety of *Zishenpingchan* granules for the treatment of PD.

Subjects and Methods

Subjects

This was a randomized, double-blind, placebo-controlled parallel study. From December 2014 to December 2016, PD patients were collected from the Department of Neurology of Longhua Hospital, and Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine in China. This study was registered in the Chinese Clinical Trial Register (registration number ChiCTR-INR-1701194). The study, which followed the *Declaration of Helsinki* and relevant Chinese clinical trial research regulations, was approved by the Ethics Committee of Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine before implementation (approval No. 2014LCSY34). Informed consent was signed before each subject was selected.

Inclusion criteria

Patients of either sex presenting with all of the following cri-

teria were considered for study inclusion:

- In western medicine, PD diagnostic criteria refers to Parkinson's disease Diagnostic Criteria (Leon-Sarmiento et al., 2013) of UK Brain Banks Network
- Hoehn-Yahr grade (Hoehn and Yahr, 1967a) ≤ 4
- Age of 50–80 years
- Volunteer, and signed informed consent

Exclusion criteria

Patients with one or more of the following conditions were excluded from this study:

- Secondary PD
- Other severe central nervous system diseases
- Serious heart, lung, kidney disease or mental illness
- History of drug or alcohol abuse
- Pregnant or lactating women

Withdrawal criteria

Patients who met one or more of the following criteria were withdrawn from this study:

- Subjects did not follow the test requirements to take the test drug
- Lost to follow-up
- Investigators advised individuals to quit because of poor adherence, severe complications, or severe adverse events
- Although the test was completed, the dose was not in the range of 80–120%
- Ventilated or emergency unblinded patients
- During the observation, subjects took drugs that cannot be converted into levodopa dosages

Sample size calculation, randomization, and blinding

The estimated curative effects of placebo and Traditional Chinese Medicine were 43.2% and 68.0%, respectively, according to the pre-experiment. Data were substituted into the formula as follows (Jenkinson et al., 1997).

$$N = \left[\frac{u_\alpha \sqrt{2\bar{P}} + u_\beta \sqrt{2(p_1 - P)(p_2 - P) / \bar{P}}}{p_1 + p_2} \right]^2$$
$$\bar{p} = (p_1 + p_2 - 2p) / 2$$

U_α and U_β were the corresponding U -values for α and β ; α was set to 0.05, β was set to 0.1. The normal distribution table was checked; $U_\alpha(0.05) = 1.96$ and $U_\beta(0.1) = 1.28$ were found. P_0 and P_1 represent the original curative effect and estimated curative effect, respectively. Assuming a patient loss rate of 10%, we required 128 patients ($n = 64$ per group).

The drugs for treatment and control groups were uniformly prepared and packaged by Jiangsu Tianjiang Pharmaceutical Company (production license: Jiangsu 20110097). SPSS 18.0 software (SPSS Inc., Chicago, IL, USA) was used to produce random numbers for each drug and a label to be pasted on the box. Subjects were allocated into treatment and control groups according to a random number table. The test drug was dispensed. This study used blinding and concealed allocation according to experimental requirements.

Implementation of blinding: (1) Two-level blind method was set up by the clinical trial leader and statistical staff.

The test drug was first set, and then the box number of the test drug was set. (2) Blind preservation: The process of setting the blind was written and signed by all staff. After the drug package was sealed, the blind was immediately given a "blind storage seal" that was kept by the clinical trial unit. (3) Emergency letters: Each numbered test drug had a corresponding emergency letter, which indicated the actual drug name and test code. Outside the envelope, the letter-keeping method was marked, as were the unpacking standard and drug code (the label of the drug, the emergency letter envelope, and the code of the drug in the emergency envelope must be consistent). (4) Unblinding: The first blind was unblinded after the researchers completed the clinical trial, and the statistical analyst completed the data management. The second blind was unblinded after statistical analysis. Finally, after the corresponding conclusion was unblinded, a statistical analysis report was formed.

Drug administration

The treatment group was given *Zishenpingchan* granules consisting of 15 g of *Radix Rehmanniae preparata*, 12 g of *Lycium barbarum*, 20 g of *Herba Taxilli*, 12 g of *Rhizoma Gastrodiae*, 9 g of *Stiff Silkorm*, 15 g of *Curcuma phaeocaulis*, 15 g of *Radix Paeoniae Alba*, 15 g of *Rhizoma Arisaematis*, 6 g of *Scorpio*, and 6 g of *Centipede*.

The control group was given Chinese medicine placebo particles containing 5% active ingredients of *Zishenpingchan* granules, as well as starch, dextrin, bitter agents. The shape, color, smell, taste, and packaging appearance were identical to *Zishenpingchan* granules.

Zishenpingchan or placebo granules 1 bag (8 g) were prescribed twice daily, in the morning and evening. Free fried granules were obtained from Jiangsu Tianjiang Pharmaceutical Co., Ltd., China (batch No. 1410302). Treatment of the two groups was performed for 24 weeks.

During treatment, dosages of PD drugs that are converted to levodopa were added or reduced (such as Madopar, Carbidopa, Levodopa CR, dopamine receptor agonists, monoamine oxidase inhibitors, and COMT2 inhibitors). Each case study was recorded. The conversion formula was 100 mg of levodopa = 10 mg selegiline = 10 mg bromocriptine = 1 mg pramipexole. Drugs that cannot be converted into levodopa dosages, such as artane amantadine, were not used.

Outcome measures

The following measurements were recorded before and 8, 16, and 24 weeks after treatment.

Primary outcome measures

The Unified Parkinson's Disease Rating Scale (UPDRS) I and IV (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003), Scales for Outcomes in Parkinson's disease—Autonomic (SCOPA-AUT) (Visser et al., 2004), Parkinson's disease sleep scale (PDSS) (Chaudhuri et al., 2002), Hamilton Anxiety Scale (HAMA) (Hamilton, 1959), Hamilton Depression Scale (HAMD) (Hamilton, 1967), Mini-Mental State Examination (MMSE) (Folstein et

al., 1983), Parkinson's Disease Quality of Life Questionnaire (PDQ-39) (Jenkinson et al., 1997), and levodopa dosage were used as primary outcome measures.

Secondary outcome measures

The UPDRS II and III (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003), on-off phenomenon, and Hoehn-Yahr grade (Hoehn and Yahr, 1967b) were used as secondary outcome measures.

Safety evaluation

We analyzed routine blood and urine tests, hepatic and renal functions (alanine aminotransferase, aspartate aminotransferase, serum creatinine, and blood urea nitrogen levels), and an electrocardiogram (ECG), and also observed the occurrence of adverse events.

Statistical analysis

The data, expressed as the mean \pm SD, were analyzed using SPSS 18.0 software (SPSS, Chicago, IL, USA). A value of $P < 0.05$ was considered statistically significant.

Intragroup comparison during each treatment was performed by first applying Mauchly's test of sphericity to determine whether there was a correlation between repeated measurement data. If there was a correlation ($P < 0.05$), data were analyzed by multivariate analysis of variance or correction results of Greenhouse-Geisser. Calculating the variability between subjects allowed for analysis of the presence or absence of treatment factors. Calculating intrasubject variability allowed for analysis of the presence or absence of time factors and the effects of interactions between the time factor and treatment factor. Multiple comparison in a repeated measures design was carried out using a paired t test (Bonferroni method) between groups at different time points. The complication between groups was conducted using multivariate analysis of variance at the beginning and 8, 16, and 24 weeks after treatment.

Quality control

We made the operation specification of this clinical trial and trained the researchers in a unified way, including how to complete the case report, charge the rating scale, grade the scales, complete the physical examination, input the data, and ensure follow-up. The professional quality controller conducted regular monitoring. Two researchers made double entry and validation of case reports to ensure uniformity of the data. The researchers were not involved in statistical analysis.

Artificial neural network methods

The effects of the treatment group's parameters on the PDQ-39 scale were evaluated by artificial neural networks. The main factors were constructed as follows:

(1) Model type: A three-layer back-propagation network was selected. (2) The transfer function was the Sigmoid function. (3) The number of neurons in the hidden layer was 10. (4) Input layer: UPDRS III, UPDRS IV, SCOPA-AUT, PDSS, HAMA, HAMD scale, and levodopa dosage were used as the input layer. (5) Output layer: The output layer

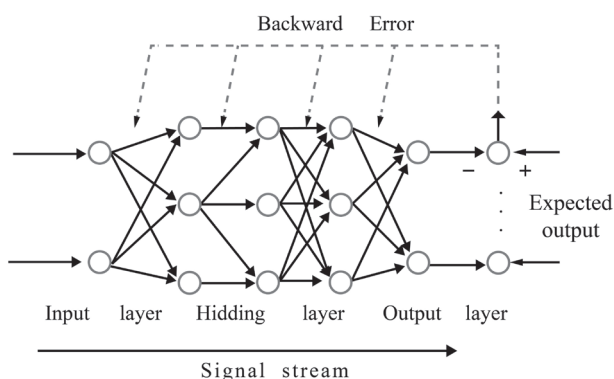


Figure 1 Mathematical description of back-propagation artificial neural network.

Input layer: UPDRS III, UPDRS IV, SCOPA-AUT, PDSS, HAMA, HAMD scale, and levodopa dosage. The transfer function was the Sigmoid function. Output layer: The output layer for the prediction of the main indicators also had a neuron.

for the prediction of the main indicators also had a neuron. After the model was established, through training and the learning of input samples, we could obtain a stable prediction and judgment model. The mathematical description (Visser et al., 2004) of our back-propagation artificial neural network is shown in **Figure 1**.

Results

Characteristics of PD patients

From December 2014 to December 2016 (commencement of enrollment to the end of clinical observation), 128 PD patients were collected from the Neurology Outpatient Departments in Longhua Hospital and Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine of China. Four patients dropped out: three patients had poor compliance and one patient could not tolerate oral administration of Chinese medicine. Finally, 124 patients completed the trial, including 63 members of the treatment group, 61 members of the control group (**Figure 2**). No significant difference was found in age, sex, history, duration, number of switching phenomena, mean daily levodopa dosage, Hoehn-Yahr grade, UPDRS scale, or non-motor symptoms scale between the groups ($P > 0.05$; **Table 1**).

Motor symptoms in PD patients treated with Zishenpingchan granules

There was no significant difference in Hoehn-Yahr grade or UPDRS II score between the two groups at the end of treatment ($P > 0.05$). Indeed, there was no significant difference in UPDRS II score at any stage ($P > 0.05$). However, the UPDRS III score was significantly lower at 24 weeks compared with before treatment in the treatment group ($P < 0.05$). Moreover, the UPDRS III score was significantly lower in the treatment group compared with the control group at 16 and 24 weeks after treatment ($P < 0.01$; **Table 2**).

Non-motor symptoms scale in PD patients treated with Zishenpingchan granules

No difference was observed in UPDRS I or MMSE scores

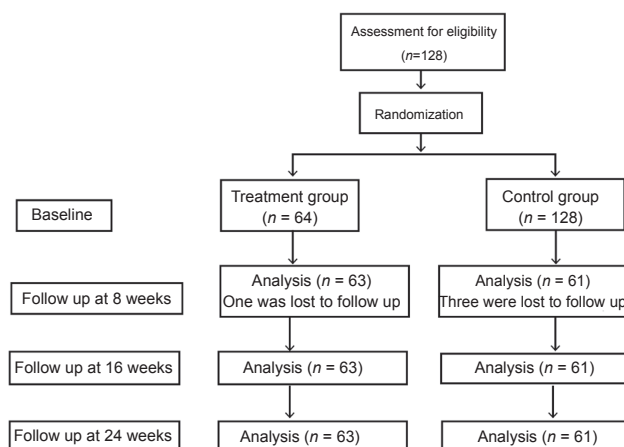


Figure 2 Flow chart of the trial.

between treatment and control groups. UPDRS I and MMSE scores were not significantly different at various time points in either group ($P > 0.05$). The control group showed no obvious difference in HAMA scores ($P > 0.05$) at various time points examined. However, HAMA scores were significantly decreased at 16 and 24 weeks compared with before treatment in the treatment group ($P < 0.05$ or $P < 0.01$). Moreover, the HAMA score of the treatment group was significantly lower compared with the control group at 24 weeks ($P < 0.01$). There was no significant difference in HAMD scores at various time points between either group ($P > 0.05$). However, the HAMD score in the treatment group was significantly lower compared with the control group at 16 and 24 weeks ($P < 0.05$). From week 16, the SCOPA-AUT score was lower, while the PDSS score was higher than before treatment in the treatment group. At 8, 16, and 24 weeks, the SCOPA-AUT score was significantly lower, but the PDSS score was higher in the treatment group than in the control group ($P < 0.05$). PDQ-39 score was significantly lower at 24 weeks than before treatment in the treatment group and compared with the control group ($P < 0.05$; **Table 3**).

Motor complications scale and levodopa dosage in PD patients treated with Zishenpingchan granules

UPDRS IV score was significantly higher at 24 weeks than before treatment in the control group ($P < 0.05$). From week 16, the UPDRS IV score in the treatment group was significantly lower than before treatment ($P < 0.05$ or $P < 0.01$). Moreover, UPDRS IV scores were significantly lower in the treatment group compared with the control group at 16 and 24 weeks ($P < 0.01$).

The "on-off period" phenomenon appeared in 34 cases of the treatment group and 36 cases of the control group. At 24 weeks, no significant difference in "on period" was observed ($P > 0.05$), while "off period" was significantly prolonged in the control group ($P < 0.05$). At 24 weeks, the "on period" was significantly prolonged and "off period" shortened in the treatment group ($P < 0.05$). Thus, compared with the control group, the "on period" was extended and the "off period" was shortened in the treatment group ($P < 0.05$).

The amount of levodopa dosage increased significantly at 24 weeks in the control group ($P < 0.05$), while there was no significant change in levodopa dosage in the treatment group at various time points examined ($P > 0.05$). At 24 weeks, levodopa dosage was significantly lower in the treatment group than in the control group ($P < 0.05$; **Table 4**).

Influence weight of each parameter variable in artificial neural networks on the PDQ-39 scale

After treatment for 24 weeks, the influence of each variable

Table 1 Baseline characteristics of participants

Item	Treatment group (n = 63)	Control group (n = 61)
Age (year)	66.77 ± 7.99	65.83±6.41
Sex (n)		
Male	33	34
Female	30	27
Course of disease (year)	7.41±3.15	6.91±3.66
Mean daily levodopa dose (mg/d)	524.98±213.19	511.89±166.38
Number of switching phenomena (n)	36	34
UPDRS		
I	3.13±1.37	3.30±1.41
II	11.38±4.42	12.11±4.84
III	18.37±6.92	18.81±6.82
IV	1.94±1.45	2.27±2.06
Hoehn-Yahr stage (n)		
2	13	15
2.5	32	27
3	12	13
4	5	6
SCOPA-AUT score	11.76±5.88	12.16±6.08
PDSS score	99.59±26.68	91.58±35.47
HAMA score	16.02±7.29	16.37±7.30
HAMD score	12.59±8.73	12.37±7.64
MMSE score	25.57±4.33	25.14±5.41
PDQ-39 score	41.37±24.78	38.08±21.77

The treatment group was prescribed 8 g *Zishenpingchan* granules twice daily, while the control group was prescribed 8 g placebo granules twice daily. Data are expressed as the mean ± SD. UPDRS: Unified Parkinson's Disease Rating Scale; SCOPA-AUT: Scales for Outcomes in Parkinson's disease—Autonomic; PDSS: Parkinson's disease sleep scale; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; MMSE: Mini-Mental State Examination; PDQ-39: Parkinson's disease quality of life questionnaire.

Table 2 Motor symptoms scale in Parkinson's disease patients treated with *Zishenpingchan* granules

Group		n	Week 0	Week 8	Week 16	Week 24
Hoehn-Yahr grade	Treatment	63	2.65±0.57	2.65±0.57	2.62±0.57	2.62±0.57
	Control	61	2.67±0.62	2.67±0.62	2.68±0.61	2.70±0.61
UPDRSII	Treatment	63	11.38±4.42	11.08±4.11	11.27±4.01	11.08±4.04
	Control	61	12.11±4.84	12.49±4.96	12.62±4.91	12.57±4.93
UPDRSIII	Treatment	63	18.37±6.92	17.43±7.12	16.57±6.75**	15.95±6.61***
	Control	61	18.81±6.82	19.40±7.20	19.78±7.02	19.95±6.99

The treatment group was prescribed 8 g *Zishenpingchan* granules twice a day, while the control group was prescribed 8 g placebo granules twice daily. Data are expressed as the mean ± SD (paired *t* test). * $P < 0.05$, vs. week 0 (before treatment); ** $P < 0.01$, vs. control group. UPDRS: Unified Parkinson's Disease Rating Scale.

on the PDQ-39 scale was calculated by comparison with differences of UPDRS III, UPDRS IV, SCOPA-AUT, PDSS, HAMA, HAMD, and levodopa dosage as input variables for the treatment group. The results showed that factors influencing the change of PDQ-39 scale pre-therapy and post-treatment in the treatment group were as follows: SCOPA-AUT scale, levodopa dosage, HAMD scale, UPDRS III, UPDRS IV, PDSS, and HAMA scores (**Table 5**).

Safety assessment in PD patients treated with *Zishenpingchan* granules

Heart rate, blood pressure, and ECG did not significantly change in 124 patients before and after treatment. Both liver and kidney function test results were within the normal range. Among the patients, 24 individuals experienced gastrointestinal flatulence, nausea, constipation, diarrhea and other gastrointestinal adverse reactions, consisting of 14 members of the treatment group and 10 members of the control group ($P > 0.05$). All adverse reactions were mild, and no patients were lost as a result of adverse drug reactions.

Discussion

For long-term clinical practice, *Zishenpingchan* granules were prepared by Professor Jianhua Hu to nourish the liver and kidney, dredge collaterals, and detoxify. *Zishenpingchan* granules exert a neuroprotective effect and the combination of *Zishenpingchan* granules and levodopa inhibited hyperactivation of extracellular signal-regulated kinase and c-Jun N-terminal kinase pathways to reduce the inflammatory reaction of substantia nigra cells and the apoptosis of dopaminergic neurons (Ye et al., 2016; Ye et al., 2017). Our results showed that *Zishenpingchan* granules had a beneficial effect for dyskinesia in PD, especially the improvement of UPDRS III scores.

This combination of Chinese and Western medicine can reduce PD motor complications, extend the on-period, shorten the off-period, and reduce the dosage of levodopa preparations. This result is positive for the prevention of complications arising for the use of levodopa for long periods of time, and terminating the progression of disease. Traditional Chinese Medicine can improve many PD non-motor symptoms, such as depression and anxiety, and especially autonomic nerve dysfunction and quality of sleep. This may be associated with the ability of *Zishenpingchan* granules to adjust striatal dopamine D1 and D2 receptor

Table 3 Non-motor symptoms scale in Parkinson's disease patients treated with Zishenpingchan granules

	Group	n	Week 0	Week 8	Week 16	Week 24
UPDRSI	Treatment	63	3.13±1.37	2.97±1.28	2.94±1.32	2.78±1.30
	Control	61	3.30±1.41	3.27±1.39	3.21±1.41	3.27±1.37
HAMA	Treatment	63	16.02±7.29	14.60±7.48	12.95±7.48*	11.92±7.94****
	Control	61	16.37±7.30	14.03±6.25	15.05±6.61	15.65±6.24
HAMD	Treatment	63	12.59±8.73	12.21±8.52	10.62±7.47#	10.97±7.46#
	Control	61	12.37±7.64	12.37±7.61	13.70±7.90	14.11±7.88
MMSE	Treatment	63	25.57±4.33	25.65±4.40	25.59±4.36	25.83±4.21
	Control	61	25.14±5.41	25.00±5.36	24.83±5.28	24.65±5.44
SCOPA-AUT	Treatment	63	11.76±5.88	10.16±4.87#	8.84 ± 4.32****	8.70±4.27****
	Control	61	12.16±6.08	12.49±5.33	13.17±5.20	13.24±5.54
PDSS	Treatment	63	99.59±26.68	105.14±25.21#	110.25±22.85***	112.14±22.22***
	Control	61	91.58±35.47	89.84±33.96	87.81±32.17	86.79±30.79
PDQ39	Treatment	63	41.37±24.78	40.43±23.36	40.76±23.32	38.30±19.77#
	Control	61	38.08±21.77	39.63±20.58	42.19±20.83	44.46±21.11*

The treatment group was prescribed 8 g Zishenpingchan granules twice a day, while the control group was prescribed 8 g placebo granules twice daily. Data are expressed as the mean ± SD (paired *t* test). **P* < 0.05, ***P* < 0.01, vs. 0 week (before treatment); #*P* < 0.05, ##*P* < 0.01 vs. control group. UPDRS: Unified Parkinson's Disease Rating Scale; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; MMSE: Mini-Mental State Examination; SCOPA-AUT: Scales for Outcomes in Parkinson's disease-Autonomic; PDSS: Parkinson's disease sleep scale; PDQ-39: Parkinson's disease quality of life questionnaire.

Table 4 Motor complication scales and levodopa dosage in Parkinson's disease patients treated with Zishenpingchan granules

	Group	n	Week 0	Week 8	Week 16	Week 24
UPDRS IV	Treatment	63	1.94±1.45	1.83±1.39	1.52±1.16***	1.38±0.96****
	Control	61	2.27±2.06	2.44±2.01	2.79±2.02	2.92±1.99*
On-period (hour)	Treatment	34	8.01±1.61	7.89±1.49	8.87±1.88	9.72±2.39**
	Control	36	7.88±1.82	7.68±2.06	7.75±2.14	7.51±2.34
Off-period (hour)	Treatment	34	4.83±1.44	4.67±1.45	4.18±1.85	3.86±1.29**
	Control	36	4.74±1.48	4.90±1.88	5.20±2.11	5.85±2.11*
Levodopa dosage	Treatment	63	524.98±213.19	525.78±213.33	519.43±199.53	521.47±192.88#
	Control	61	511.89±166.38	523.00±174.34	538.08±165.17	589.52±177.21*

The treatment group was prescribed 8 g Zishenpingchan granules twice a day, while the control group was prescribed 8 g placebo granules twice daily. Data are expressed as the mean ± SD (paired *t* test). **P* < 0.05, ***P* < 0.01, vs. 0 week (before treatment); #*P* < 0.05, ##*P* < 0.01, vs. control group. UPDRS: Unified Parkinson's Disease Rating Scale.

Table 5 Influence weight of each parameter variable in artificial neural networks on the PDQ-39 scale

	PDQ-39 < -28.17	PDQ-39 = -28.17 to -14.79	PDQ-39 = -14.79-7.54	PDQ-39 = -7.55 to -0.054
1	SCOPA-AUT = -1.68 to -0.24 (95.95)	UPDRS III = -6.34 to -5.47(100)	PDSS = 21.79-28.27(97.82)	HAMA < -15.48(100)
2	Levodopa dosage < -256.25(69.01)	UPDRS III < -13.34(66.61)	UPDRS IV = -2.1 to -0.2(50.4)	SCOPA-AUT = -1.68 to -0.24(88.74)
3	HAMD < -8.23(48.94)	UPDRS IV < -4(53.27)	PDSS = 4.55-8.86(28.61)	UPDRS IV = -4 to -2.1(65.81)
4	SCOPA-AUT ≥ -0.24(30.52)	SCOPA-AUT < -9.27(50.35)	UPDRS III = -13.34 to -6.34(27.75)	UPDRS IV < -4(53.46)
5	HAMA ≥ -1.42(30)	UPDRS IV = -2.1 to -0.2(41.78)	HAMA ≥ -1.42(27.24)	HAMD = -3.39 to -1.21(39.34)
6	UPDRS IV ≥ -0.20(20.7)	SCOPA-AUT = -9.27 to -4.33(36.72)	HAMD = -8.23 to -3.39(20.03)	PDSS = 8.86-21.79(36.86)
7	PDSS < 4.55(20.52)	HAMA = -8.95 to -6.55(33.11)	SCOPA-AUT = -9.27 to -4.33(36.72)	HAMA = -15.48 to -8.95(22.97)
8	UPDRS III = -13.34-6.34(15.75)	PDSS ≥ 28.27(32.36)	SCOPA-AUT = -4.32 to -1.68(23.75)	SCOPA-AUT ≥ -0.24(21.09)
9	HAMA < -15.48(9.76)	HAMD ≥ 0.71(30.63)	HAMD ≥ 0.71(30.63)	UPDRS III ≥ -0.66(19.31)
10	UPDRS III = -5.47 to -0.66(8.84)	Levodopa dose = 18.75-43.75(23.86)	HAMD < -8.23(19.91)	PDSS ≥ 28.27(15.6)

The treatment group was prescribed 8 g Zishenpingchan granules twice daily. Numerical value represents the variable at 24 weeks after treatment minus the relevant variables before treatment in the treatment group. Considering PDQ-39 difference as a prediction variable, differences of UPDRS III, UPDRS IV, SCOPA-AUT, PDSS, HAMA, HAMD and levodopa dosage are used as input variables in artificial neural networks. PDQ-39 is divided into four ranges: PDQ-39 < 28.17, PDQ-39 = 28.17-14.79, PDQ-39 = 14.79-7.54 and PDQ-39 = 7.54-0.054. The biggest impact of the top ten factors was analyzed. UPDRS: Unified Parkinson's Disease Rating Scale; HAMA: Hamilton Anxiety Scale; HAMD: Hamilton Depression Scale; SCOPA-AUT: Scales for Outcomes in Parkinson's disease-Autonomic; PDSS: Parkinson's disease sleep scale; PDQ-39: Parkinson's disease quality of life questionnaire.

gene expression and receptor activation, thus improving the imbalance between direct and indirect pathways in basal ganglia, and reducing the stimulation of levodopa on post-synaptic membrane to prolong its efficacy (Ye et al., 2014b).

In this study, PDQ-39 score obviously increased in the treatment group compared with the control group, clearly demonstrating that the Chinese medicine improved the living condition of PD patients. This may be attributable to the improvement of both motor and non-motor symptoms by the Traditional Chinese Medicine. Nevertheless, the improvement of a single scale does not directly enhance the quality of daily life. Thus, the artificial neural networks statistical model was used to analyze differences in UPDRS III, UPDRS IV, SCOPA-AUT, PDSS, HAMA, HAMD and levodopa dosage as input variables; the results showed improvement of the treatment group compared with the control group. Considering the impact of these variables on PDQ-39, our results showed that *Zishenpingchan* granules mainly improved autonomic nerve dysfunction and depression, and reduced levodopa dosage to increase PDQ-39 in PD patients – suggesting that *Zishenpingchan* granules improved the quality of daily life. As the primary limitation of this study is that only a Han population from a single region is included, double-blind randomized control trials of high quality, with large sample numbers and adequate follow-up of different ethnic groups in different regions are required for further verification.

Author contributions: QY conceived and designed the study. QY and XLY performed the experiments and wrote the paper. CXY, HZZ and XMY reviewed and edited the paper. QY and CXY were in charge of the funds. CXY and XMY provided technical and information support. All authors approved the final version of the paper.

Conflicts of interest: The authors declare that they have no conflicts of interest.

Financial support: This study was supported by a grant from Major Project of Shanghai Committee of Science and Technology of China, No. 15401970100; a grant from the National Natural Science Foundation of China (General Program), No. 81673726; a grant from the Project of Shanghai Committee of Science and Technology of China, No. 17401934600; a grant from Longhua Scholar Plan of National Traditional Chinese Medicine Clinical Base of China, No. LYTD-34; a grant from Shanghai Traditional Chinese Medicine Science and Technology Innovation Project, No. ZYKC201601002. The funding bodies played no role in the study design, in the collection, analysis and interpretation of data, in the writing of the paper, or in the decision to submit the paper for publication.

Institutional review board statement: The study followed the Declaration of Helsinki and was approved by the Ethics Committee of Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine before implementation (approval No. 2014LCSY34). This study has been registered in the Chinese Clinical Trial Register (registration No. ChiCTR-INTR-1701194).

Declaration of patient consent: The authors certify that they obtained all appropriate patient consent forms. In the form, the patients gave their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Data sharing statement: Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices) will be in particular shared. Study protocol and informed consent form will be available. The data will be available immediately following publication without end date.

Plagiarism check: Checked twice by iThenticate.

Peer review: Externally peer reviewed.

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Open peer review report:

Reviewer: Sanusi Mohammad Bello, King Faisal University, Saudi Arabia.

Comments to authors: The article is strong in that it for the first time addressed the challenging question of how to treat movement disorders especially Parkinson's disease.

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(Copolyedited by Van Deusen A, Raye W, Yu J, Li CH, Qiu Y, Song LP, Zhao M)