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REVIEW

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Effect of Acupuncture on the Motor and Nonmotor Symptoms in Parkinson's Disease—A Review of Clinical Studies

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SUMMARY

Parkinson's disease is a neurodegenerative disorder. Parkinson's clinical feature is characterized by its motor manifestations, although its many nonmotor symptoms occur earlier and have more profound impact on the quality of patient's life. Acupuncture has been increasingly popular and has been used to treat patients with Parkinson's. In this article, we have studied the clinical reports of acupuncture treatment for Parkinson's, which were listed in Medline, PubMed, EMBASE, CNKI, and CINAHL databases in the past 15 years. It was found that acupuncture either manual or electroacupuncture stimulation at specific acupoints relieved some motor symptoms in patients with Parkinson's and markedly improved many nonmotor symptoms such as psychiatric disorders, sleep problems, and gastrointestinal symptoms. When it was used as an adjunct for levodopa, acupuncture improved therapeutic efficacy and reduced dosage and the occurrence of side effects of levodopa. However, the results were constrained by small sample sizes, methodological flaws, and blinding methods of studies. Although the evidence for the effectiveness of acupuncture for treating Parkinson's is inconclusive, therapeutic potential of acupuncture seems quite promising. More studies, either comparative effectiveness research or high-quality placebo-controlled clinical studies are warranted.

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Introduction

Parkinson's disease (PD) is an age-related, progressive neurodegenerative disorder. It affects one in a thousand people over 60 years of age and is a substantial source of economic cost. Although both genetic and environmental factors are implicated in the development of PD, the cause of disease is still unclear. The clinical manifestation of PD motor symptoms includes bradykinesia, resting tremor, rigidity of muscles and joints, gait, and posture imbalance. The occurrence of motor symptoms is mainly caused by the severe loss of dopaminergic neurons in the substance nigra of middle brain and subsequent depletion of dopamine in the striatum [1,2]. The nonmotor symptoms of PD are found in the vast majority of patients with PD, consisting of autonomic dysfunction, neuropsychiatric disturbance, sleep disorders, gastrointestinal symptoms, and many others [3–5]. The nonmotor symptoms of PD and related disorders usually respond poorly to dopaminergic treatment. This indicates, in addition to the loss of dopamine, the changes in other neurotransmitters, such as serotonin, norepinephrine, and gamma-aminobutyric acid (GABA) and glutamate, in the different brain regions and peripheral nervous systems, are involved in the pathogenesis of many nonmotor symptoms [6]. There is currently no cure for PD. The prevalence medication for motor symptoms, such as dopamine replacement therapy, in particular levodopa treatment, is only symptomatic relief with limited effect, but has many adverse effects, for example, dyskinesia [7–9].

Acupuncture has been used to treat many conditions in China for more than 3000 years. Acupuncture is now one of the most popular complementary medicines and is used for the treatment of a variety of disorders worldwide. In general, acupuncture needle inserted at the specific acupoint stimulates nerve receptors both directly or indirectly, through mechanical coupling via the connective tissues surrounding the needle, then through the local reflex and the central nervous system, induces endocrine, neuroendocrine, autonomic, and systemic behavioral responses [10,11]. This suggests that acupuncture therapy beneficially affects a whole body even if it stimulates, through the fine needles, only limited sites on the body. Within past a few decades, acupuncture has become increasingly popular with both public and medical professionals, and it has been reported to be a very safe and well-tolerated therapy with only minor side effects [12–14]. Many patients with PD are reported using acupuncture as an alternative treatment at some points of their life. Indeed, it has been estimated that more than a quarter of patients with PD in the United States (40%), Britain (38.7%), Sweden (34.5%), Sin-

gapore (61%), and Argentina (25.7%) have used at least one form of complementary medicine, while 7–49% of them have used acupuncture as an alternative therapy [15–19]. Many patients with PD experienced improvement of their conditions after acupuncture.

Recently, we have assessed the recent research development regarding the effects and mechanisms of acupuncture on PD models [20]. In this article, we have reviewed the clinical acupuncture studies of Parkinson's and evaluated the effect of acupuncture therapy on motor and nonmotor symptoms in patients with PD.

Materials and Methods

Criteria for Considering Studies for Review

This review included the clinical studies that focused on the effect of penetrating acupuncture, with either manual or electrical stimulation, on patients with PD, without limitation on age, gender, duration of condition, and medication. The control included placebo, medication, or no treatment. Outcome measures included (1) PD motor symptom impairment rating scales; (2) PD nonmotor symptom impairment rating scales; (3) PD activity of daily living rating scales; (4) quality-of-life measures for PD; (5) changes in levodopa dose; and (6) alterations in functional neuroimaging and biochemical studies. Language restrictions were applied to English and Chinese.

Search Methods for Identification of Studies

The following electronic databases were searched in December 2014 for publications between 2000 and 2014: (1) PubMed; (2) MEDLINE; (3) EMBASE; (4) CNKI, and (5) CINAHL. The reference list of relevant studies and reviews was manually searched to identify more potential papers. The search term used in the studies was cross-referenced acupuncture and its proprietary names, and PD and with its derivations.

Study Selection and Data Extraction

The titles and abstracts of collected studies were scanned to select potential reference. Relevant articles with potential for eligible studies were selected after reviewing full text, and then, data describing patients, duration and severity of condition, treatment, control groups, and outcomes were extracted.

A total of 176 studies were identified from the electronic databases and hand searching. After searching titles and abstracts, 142 studies were excluded due to the following reasons: (1) the studies were nonclinical; (2) the studies were irrelevant to PD; (3) the studies were irrelevant to acupuncture; (4) the studies were case report; (5) patients included were not typical idiopathic PD; and (6) the studies did not show valid outcome measures. Having evaluated full text of remaining 34 literatures, 14 were selected for this study based on predefined criteria. Among the selected studies, four were conducted in the United States, two originated from Korea, and eight were from China (Table 1). The screen process was summarized in a flow diagram (Figure 1).

Effect of Acupuncture on Motor Symptoms of Parkinson's Disease

During past 15 years, there are an increasing number of clinical studies of acupuncture therapy in PD (Table 1). Cristian et al. [21] conducted a randomized controlled blind study with 14 PD patients. The patients were treated with electroacupuncture, 20 min/day, five sessions a week for 2 weeks. The data showed a trend toward significant improvement in motor scores on the Unified Parkinson's Disease Rating Scores (UPDRS) III (motor function assessment). This was accompanied by the improved activities of daily living and decreased body discomfort compared to the nonelectroacupuncture group. Using scalp acupuncture, Jiang et al. [22] carried out a randomized controlled clinical study in which 30 patients with PD were divided into two groups. Patients in treatment group were given scalp electroacupuncture for 30 min, once a day, 5 times a week for total 6 weeks, plus medication Madopar. Patients in control group were only given Madopar. The UPDRS and Webster scores were used to assess the functional changes before and after acupuncture treatment. It was found that tremor, rigidity, and bradykinesia were improved compared with base lines in both groups, respectively. However, patients in scalp acupuncture group showed more significant improvement in motor function than those of control group judged by UPDRSIII scores [22]. In another study, 38 patients with PD were divided into acupuncture plus drug group and drug control group. Patients in acupuncture group were treated with scalp acupuncture and body acupuncture for 30 min, once every 2 days, 10 times as a course and four courses in total, plus medication Prolopa. Patients in control group were only given Prolopa. At the end of treatment, total UPDRS scores were significantly reduced in acupuncture group compared with baseline scores and with scores of control group [23]. In a long-term study, 30 PD subjects, with diminished therapeutic effect and drug-induced complications, were treated with combination of scalp acupuncture and body acupuncture [24]. Acupuncture was given once every second day for 10 days as one course of the treatment, after 7 days interval, next course of treatment was followed and total treatment was for 6 months. By the end of treatment, Webster score assessment showed that acupuncture produced a remarkable effect in four cases, effective in 16 cases, and failed to show improvement in 10 cases and total effective rate was 66.7% compared with baseline scores. Further, therapeutic effects of levodopa were enhanced, while its dose and complications being reduced [24].

In a large clinical study [25], 80 PD subjects were divided into treatment group (n = 50) and control group (n = 30), it was found that acupuncture treatment for 4 weeks produced a significant improvement in motor function including tremor and gait disturbance compared to control group; however, the study did not mention how the motor functions were assessed [25]. Using functional magnetic resonance imaging (fMRI) technique, Chae et al. [26] explored the neural mechanism of specific effect of acupuncture stimulation on the motor function of patients with PD. When acupuncture stimulation at acupoint GB34 on patients with PD, fMRI revealed the activation of the putamen and primary motor cortex. The patients experienced a significant

Table 1 Summary of included acupuncture clinical studies

Study	Design, Sample size, Study duration	Characteristics	Acupoints	Intervention	Control	Outcome measures: Motor symptoms	Nonmotor symptoms	Others
Shulman, 2002	Uncontrolled open label, N = 20 (1) N = 7, 5 weeks (2) N-13, 8 weeks	Age: 68 years Duration: 8.5 years H&Y: 2.2 UPDRS: 38.7 Medication: N/A	Body AP: LI4, GB34, ST36, K3, K7, SP6, SI3, TB5 Scalp AP: chorea trembling control area	PD medication + body AP + scalp AP 60 min, twice a week for 5 or 8 weeks	N/A	UPDRS I to IV+, Total UPDRS+ H&Y+	Sleep and rest+++	
Cristian, 2005	Randomized Controlled Double blind, N = 14, 2 weeks	Age: 72–74 years Duration: N/A H&Y: 2–4 UPDRS: N/A	Body AP: K3, K10, L3, ST41 ST36, GB34, Bafeng points, MH6, LI4, GV20	PD medication + body EA, 4 Hz for 20 min, 5 sessions, for 2 weeks (n = N/A)	PD medication + stimulation of nonacupoints, for 20 min, 5 sessions for 2 weeks (n = N/A)	UPDRS III+ to ++	ADLs, PDQ-8 Summary Index score++; depression, nausea, sleep problems++; orthostasis-	
Eng, 2006	Uncontrolled open label, N = 23, 24 weeks	Age: 69.3 years Duration: 6.4 years H&Y: 2.1 UPDRS: 37.8 Medication: N/A	Body AP: ST 42, SP 3, LI11, LI15, LI20, ST7, ST36	PD medication + energy massage (tui na) + AP for 7–10 min, Once a week for 24 weeks + Qigong machine (n = 23)	N/A	UPDRS III-	PDQ-39 + ++, BDI+++	
Jiang, 2006	Randomized controlled, N = 30, 6 weeks	Age: 65.6 years Duration: 6.0 years UPDRS: N/A Webster: 16.4 (AP), 15.3 (C)	Scalp AP: MS4, MS6, MS8, MS9, MS14	Madopar + scalp EA, 100 Hz, for 30 min, 5 times/week, total 6 weeks	Medopar 125–250 mg/each, 3–4 times/day	UPDRS III+++	Constipation+++, Sweating+++	
Yang, 2006	Controlled open label, N = 38, 68 days	Age: N/A Duration: N/A UPDRS: N/A Medication: Prolopa	Body AP: LI4, SI3, LI5, SI6, LI11, PC3, LU5, LR3, ST41, KI3, GB34, SP9, BL40, GB30 Scalp AP: MS1, MS5, MS6	Prolopa + body AP + scalp AP 30 min, 1 course = 5 AP, once every 2nd day for 10 days, 7 days interval, then next course, total 4 courses	Prolopa 62.5–500 mg/each, 2–4 times/day	Total UPDRS+++	N/A	SOD↑+++ LPO↓+++
Zou, 2006	Uncontrolled open label, N = 30, 6 months	Age: 47–81 Duration: 1–16 H&Y: II=6, III=9, IV=12, V = 3	Body AP: GV14, GV20, GV26, GB20, TE17, ST36, ST40, SP6, KI3, LR3	Madopar + body AP + scalp AP, 1 course = 5 AP, once every 2nd	N/A	Webster scores +++ (n = 4), ++ (n = 16), +-0 (10),	Constipation+++	Madopar dosage reduced after AP

(continued)

Table 1 (Continued)

Study	Design, Sample size, Study duration	Characteristics	Acupoints	Intervention	Control	Outcome measures: Motor symptoms	Nonmotor symptoms	Others
		Medication: Madopar 0.5–1.25 g	Scalp AP: dance and tremor zone	day for 10 days, 7 days interval, then next course for total 6 months		total effective rate: 66.7%. Madopar reduction+		
Ren 2008	Controlled, N = 80, 4 weeks	Age: N/A Duration: N/A UPDRS: N/A	Body AP: TE4, LI5, PC7, SI6, LI11, LU5, PC3, HT3, TE14, LI15, SI9, LR4, KI3, ST41, SP9, GB34, BL40, GB30, BL36	Madopar 752 mg ± 159 + AP 30 min, once a day for 10 days as a session, interval 3–5 days, and another session	Madopar 749 ± 169	Tremor++, Gait++	N/A	Madopar dosage: AP: 504 ± 179 Control: 726 ± 261
Chae, 2009	Randomized single blind uncontrolled, N = 10, 1 time	Age: 45–66 years Duration: 3.0 ± 2.0 years H&Y: 1.6 ± 0.2 UPDRS: 33.0 ± 15.5	GB34	AP for 9 min	Placebo	Finger-tapping task+++	N/A	fMRI showed AP increased activation in the putamen and the motor cortex
Chen, 2012	Randomized Controlled, N = 60 6 weeks	Age: N/A Duration: N/A UPDRS: N/A	GV20, EX-HN 3, EX-HN 1	AP + Madopar + Tolterodine 1 mg, 2 times/day	Madopar + Tolterodine 2 mg, 2times/day	UPDRS III+++	Bladder function+++	
Cho, 2012	Randomized single blind controlled, N = 22, 8 weeks	Age: 55–57 years Duration: 5–6 years H&Y: 1.6–3.0 UPDRS: 33.0 ± 15.5	GB20, LI11, GB34, ST36, LR3	(1) PD medication + VA, 2 times weekly for 8 weeks (n = 13) (2) PD medication + AP (rotated at 2 Hz for 10s, and maintained for 20 min), 2 times weekly for 8 weeks (n = 13)	PD medication only (n = 9)	Total UPDRS+++ UPDRS III+++	BDI+++	
Xia, 2012	Randomized Controlled, N = 60, 12 weeks	Age: N/A Duration: N/A UPDRS: N/A	GV20, EX-HN 3, EX-HN 1, LR3, SP6	Madopar+fluoxetine + AP for 12 weeks	Madopar+fluoxetine	N/A	Depression+++	Serum BDNF+++
Lei, 2014	Randomized Controlled, N = 13, 3 weeks	Age: N/A Duration: N/A UPDRS: N/A	N/A	EelctroAP 30 min, once a week for 3 weeks	Sham	Balance+++, gait+++, postural transitions+++	N/A	

(continued)

Table 1 (Continued)

Study	Design, Sample size, Study duration	Characteristics	Acupoints	Intervention	Control	Outcome measures: Motor symptoms	Nonmotor symptoms	Others
Yuan, 2014	Controlled, Open label, N = 49, 3–6 weeks	Age: N/A Duration: N/A UPDRS: N/A	DU15, bilateral BL10, GB20, GB12	EelctroAP 30 min, 3 times a week for 3 to 6 weeks + Madopar	Madopar 250 mg, 3 times/day	Webster scale ++ to +++	N/A	87% of patients stopped medication for 2 weeks after AP
Liang, 2014	Controlled, Open label, N = 70, 24 weeks	Age: 48–73 years Duration: 3–7 years H&Y: 1.0–3.0 UPDRS: 33.0 ± 15.5	Bilateral GB20, GB12, BL10; GV15	(1) AP, 30 min/each time, 3 times weekly for 24 weeks (n = 35)	Madopar 250 mg, 3 times/day, for 24 weeks (n = 35)	PDQ-39 + ++	UPDRSII+++ PDSS+++ PDQ-39 + ++	

AP, acupuncture; N, numbers; UPDRS, Unified Parkinson's Disease Rating Scale; N/A, not available; min, minute; S&E ADLs, Schwab and England Activities of Daily Living; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; PDQ-39, Parkinson's Disease Questionnaire; PDSS, Parkinson's disease sleep scale; H&Y, Hoehn and Yahr stage; fMRI, functional magnetic resonance imaging; SOD, superoxide dismutase; LPO, lipid peroxides; BDNF, brain-derived neurotrophic factor. ↑, increase; ↓, decrease; +, indicates minor improvement; ++, indicates median improvement; +++, indicates significant improvement. -, indicates worsening effect.

improvement of motor function, finger-tapping tasks of affected hand following acupuncture [26]. This suggested that acupuncture exerted its beneficial effect via its ability to modulate neuronal activities in the specific motor-related brain regions in patients with PD.

Recently, Chen et al. [27] conducted a clinical study of acupuncture treatment with PD patients. Sixty PD subjects were randomly divided into two groups: patients in treatment group were treated with electroacupuncture once a day plus Madopar for 6 weeks; patients in control group were given Madopar only. By the end of 6-week treatment, the UPDRSIII assessment showed that acupuncture produced a significant improvement in motor function with reduced adverse effect compared to Madopar alone group [27]. Similarly, Cho et al. [28] reported, in a randomized controlled clinical study with 43 PD patients, that acupuncture treatment twice a week for 8 weeks significantly improved UPDRS total scores and UPDRSIII scores in patients with PD, while control group did not show any significant improvement in any outcome.

Very recently, a small randomized controlled clinical study was conducted to evaluate the efficacy of electroacupuncture for improving gait and balance in patients with PD using objective modalities based on innovative body worn sensors technology [29]. Thirteen patients with PD were randomly treated with real acupuncture (n = 10) or sham acupuncture (n = 3) for 30 min, once weekly for 3 weeks. Assessments, measured before and after treatment, include gait, balance, and postural transitions. By the end of treatment, acupuncture group showed a significant improvement in gait, balance, and UPDRSIII compared to baseline. No difference was found in control group compared to baseline. Group comparison revealed that balance, gait speed, and stride length during all conditions was significantly improved in acupuncture group compared to control group [29].

The acupuncture technique called "the seven acupoints of cranial base" (SACB) was used as the adjunct to treat patients with PD in China recently and showed some interesting results. The SACB consists of DU15, bilateral BL10, GB20, and GB12 which are believed to be located at the very place of cranial bottom [30]. In an uncontrolled open labeled clinical study, 49 patients with PD were recruited and categorized as early (<10 scores, n = 4), moderate (11–20 scores, n = 43), and advanced stage (21–25 scores, n = 2) according to the Webster scores. All patients were treated with electroacupuncture at the "seven acupoints" for 30 min, 3 times a week. Then, the courses of acupuncture treatment were decided according to the severity of condition. After the initial three acupuncture treatments, patients with early stage were asked to stop medication, then treated with acupuncture for further 6 times (total nine treatments within 3 weeks). Patients with moderate stage, after the first three acupuncture treatments, were asked to reduce medication to half dose; after given further three acupuncture treatments, they were asked to stop medication, then given further six acupuncture treatments (total 12 treatments within 4 weeks). For advanced stage, patients, after the initial three acupuncture treatments, were asked to reduce the dose of medication by one-third, then after further six acupuncture treatments, were asked to reduce the dose by half on the base of first reduced dose; after one further treatment, patients were asked to stop the medication and were given further nine acupuncture treatments (total 19 treatment within 6 and half

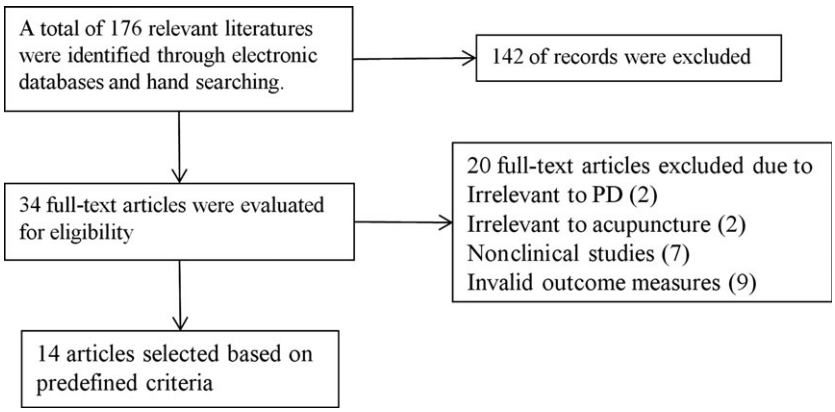

Figure 1 Flowchat of study selection.

weeks). Before acupuncture, the average of Webster score was 16.74 ± 3.35, and it was significantly reduced to 11.50 ± 4.17 after acupuncture treatment. Approximately 87% of patients with PD stopped medication for two weeks after last acupuncture treatment and maintained good improvement of their symptoms [30]. It would be very interesting to know the outcome of the follow-up study.

Taken together, the studies mentioned above demonstrated that acupuncture including scalp acupuncture ameliorated motor symptoms in patients with PD. How does acupuncture exert its motor function improvement is not well studied in clinical setting. However, many basic studies shed light on the mechanism of acupuncture on motor function, review see [20]. It has been reported that acupuncture stimulation at specific acupoints markedly reduced rotational behavioral, significantly reduced the loss of dopaminergic neurones, and significantly elevated expression of TrkB in the lesioned substantia nigra [31,32]. Acupuncture also significantly increased tyrosine Hydroxylase-immunoreactive fiber density in the lesioned striatum [33] and markedly reversed decrease in superoxide dismutase and glutathione peroxidize, while decreased the increase in the levels of malondialdehyde, tumor necrosis factor-alpha and interleukin-1 in the brain nigrostriatal system [32,34]. These studies indicated that acupuncture protected dopaminergic neurons against toxic insults and increase dopamine production in the brain by inducing release of neurotrophic factor, enhancing antioxidant agents, and inhibit inflammatory.

Effect of Acupuncture on Nonmotor Symptoms of Parkinson's Disease

Nonmotor symptoms (NMSs) of PD are common but are often under-recognized in clinic practice due to the lack of spontaneous complaints from patients. NMS in PD was systematically reviewed for the first time by Chaudhuri et al. [3]. NMS ranges from autonomic dysfunction, neuropsychiatric disorders, sleep disturbance, sensory symptoms to gastrointestinal syndromes, fatigue, and many others and are often under-treated [3]. NMS occurs throughout the course of the disease. Some of them, such as depression, fatigue, and smelling dysfunction, may appear at the earliest stage of the disease in un-treated patients. Others appear at the advanced stage of the disease. At the time of diagnosis, the prevalence of NMS among patients with PD was 21% (pain, urinary symptoms, depression, and anxiety) and went up to 88% after 7-year disease progression [14,35]. Indeed, nonmotor aspects of PD had greater impact on quality of life and cause higher institutionalization rates and healthcare cost [36].

Psychiatric Disorders

Depression was one of the most common psychiatric symptoms in nonmotor features in PD [37]. Studies indicated that approximately 17–50% of patients with PD had depression [4,38]. Patients with depression felt sad, anxiety, irritable, and restless and might lose interest in activities once enjoyable. The cause of depression in PD was not clear, but the altered levels of serotoninergic, noradrenergic, and dopaminergic neurotransmission in brain were implicated as relevant factors [39–41]. In acupuncture clinical studies, one of the prominent responses to acupuncture in patients with PD was the reported therapeutic effect on depression [21,28,42,43]. Many patients experienced great alleviation in their symptoms. This was reflected on the results of Beck Depression Inventory, one of the most widely used instruments for measuring severity of depression, which showed a significant decrease in the scores in patients after acupuncture therapy compared with control groups [21,28,42,43]. Acupuncture is very effective in treating depression in patients without PD. Clinical studies showed that acupuncture was superior to drug treatment in reducing depression, anxiety in non-PD patients with psychiatric disorders [44,45].

Sleep Disorders

Excessive daytime somnolence (EDS) and insomnia are common symptoms of sleep disturbance of NMS in PD, affecting up to 50% or even higher proportion of patients [4,46]. Sleep disorders are more frequent in patients with advanced stage of disease and have large impact on the quality of life of patients. The occurrence of EDS is often associated with long-term medication of dopamine agonist, in particular, levodopa [47]. Acupuncture was reported to effectively improve sleep disorders in patients with PD. Acupuncture study with 20 PD patients showed that 85% of patients treated with acupuncture reported a subjective improvement in sleep problems and this was confirmed by the improvement in the sleep and rest category of the Sickness Impact Profile scores [14]. In another randomized controlled double-blind study, patients with

PD receiving electroacupuncture showed a significant improvement in sleep problems [21]. Very recently, a controlled clinical study with 70 PD patients reported that "the Seven Acupoints of the Cranial Base" acupuncture technique significantly improved sleep in patients judged by Parkinson Disease Sleep Scale (PDSS) compared with control group [48]. In non-PD patients, intradermal acupuncture on HT7 and PC6 stabilized the sympathetic activities and improved insomnia in stroke patients [49]. Acupuncture stimulation at PC6, HT7, and ST36 acupoints, commonly used to treat insomnia in clinic, increased GABA levels and elevated the expression of GABA(A) receptor in hypothalamic neurons of insomnia rats [50]. This may explain the insomnia-relieving effect of acupuncture. The results of those studies suggest that improvement of sleep disorders by acupuncture is potentially mediated by a variety of neurotransmitters including GABA, norepinephrine, melatonin, and beta endorphin, (for review, see [51]).

Gastrointestinal Symptoms

Gastrointestinal dysfunctions in PD included dysphagia, nausea, bloating, constipation, and many others [3,52]. Nausea occurred the most often due to dopaminergic therapy; however, it may occur in untreated patients [53]. Constipation is the most prominent manifestation of lower gastrointerestinal dysfunction in PD, and it may precede the development of motor symptoms of PD by many years [53,54]. Many studies showed that acupuncture treatment to patients with PD improved gastrointestinal symptoms, such as nausea and constipation without inducing any adverse effect [21,22,24]. It was reported that the effect of acupuncture on gastrointestinal dysfunction was related to its activation of various brain nuclei, such as the nucleus tractus solitaries, dorsal motor nucleus of vagus, and periaqueductal gray, through modulating the imbalance between sympathetic and parasympathetic activity of those nuclei [55]. Similarly, acupuncture markedly relieved gastrointestinal symptoms such as constipation, irritable bowel syndrome, and functional dyspepsia in patients without PD [56–58].

Autonomic Symptoms

Bladder dysfunction (urinary urgency/frequency) was one of the most common autonomic symptoms, and it occurred in 55–80% of patients with PD [59]. Urinary disturbance can appear early in the disease, and symptoms get worse with increased motor disability [35]. Recently, a clinical acupuncture study of Parkinson's with overactive bladder syndrome was conducted to assess the therapeutic effect of acupuncture as an adjunctive on bladder function [27]. It was found that at the end of 6-week treatment, acupuncture significantly improved the average frequency urination of 24 h, frequency of incontinence of 24 h, and average urine volume at a time, compared with the scores obtained prior to treatment; the improvement of urinary function in acupuncture plus drug treatment group was significantly better than those of drug alone group [27]. It was suggested that the therapeutic effect of acupuncture on bladder dysfunction might be attributed to its modulation on autonomic system and central cholinergic activity [60]. In non-PD patients, electroacupuncture treatment significantly improved chronic bladder dysfunction in patients with traumatic spinal cord injury [61] and had a long-lasting reduction of blood pressure in patients with mild-to-moderate hypertension [62].

Many clinical and basic studies reported that acupuncture including manual and electroacupuncture modulated the transmission of dopamine, noradrenalin, serotonin, glutamate, GABA; and the activation of hypothalamic–pituitary–adrenal axis within central nervous system and peripheral nervous system [51,55,63]. These effects may be attributed to the improvement of PD nonmotor symptoms by acupuncture.

Discussion

Present study reviewed the data of 519 patients with PD from 14 clinical studies. The results from some of the included studies showed the potential benefits of acupuncture for treating PD, especially nonmotor symptoms seems to be more beneficial from acupuncture treatment. However, many methodological flaws presented in most studies limited the reliability of results. Therefore, the results included in this study should be interpreted with cautious.

Outcome measures for motor symptoms differed among the included studies. For example, seven studies used the UPDRS, two studies used Webster scale, and another five studies only described changes in individual motor symptom. Among seven studies used UPDRS, four studies showed moderate to marked improvement in UPDRS III motor scores before and after acupuncture, between acupuncture plus medication and medication alone groups. One study showed negative outcome in UPDRS III motor scores [42], and two studied presented minor to moderate improvement in total UPDRS scores. Two studies used Webster scale presented marked improvement in motor symptoms. Five of 14 studies described changes in individual motor symptom following acupuncture treatment. For example, Lei et al. [29] described the improvement in balance, gait, and postural transition following acupuncture. It is difficult to draw a valid comparative conclusion based on inconsistent outcome measures. Suitable outcome measures such as UPDRS should be applied as a standard outcome measure and full data on outcome measures including mean and standard deviation should be presented.

Although many of included studies showed a moderate to marked improvement in motor function, one study [42] reported a worsening in UPDRS motor scores (24.0 vs. 26.4, $P = 0.018$). In this study, patients with PD were given acupuncture treatment for 7–10 min, once a week for 6 months [42]. However, patients in majority of included studies were given acupuncture for 20–60 min, 2–3 times a week. This implied that duration and frequency of intervention might play an important role in the outcome of treatment.

Although many nonmotor symptoms occur even before the appearance of motor symptoms, only 9 of 14 studies reported presence of the nonmotor symptoms. This is not surprise as patients do not spontaneously complain their nonmotor symptoms to doctors [3]. Within nine studies, depression was the most reported symptom, followed by sleep disorder, constipation, and bladder dysfunction. This is consistent with other studies showing depression is one of the most complained nonmotor symptoms from patients with PD [37,38]. All studies reported that acupuncture significantly improved depression of patients with PD. Beck's Depression Inventory (BDI), PDQ-39, and PDQ8 were applied to rate the changes in

depression within different studies. This led to difficult for comparison as each instrument covered different aspect of item and made the data less reliable. Similarly, the outcome of sleep disorder was measured by PDSS and ISI scores between studies. Outcome measures for other NMS were barely mentioned by relevant studies. Indeed, there is a need to achieve an agreement on what are the accepted outcome measures for NMS in PD.

Complete lack of control group occurred in 3 of 14 included studies. It has been known that the demonstration of efficacy of new treatment is based on comparing the response in the treated group with that of control group receiving placebo or another treatment. Without control group, it is very unlikely to have a reliable comparison of different treatments. Within other 11 studies, one used placebo control and another one used sham control and the remaining nine studies chosen PD medication as controls. It has been suggested that comparing acupuncture plus drug treatment with drug only may generate false favorable therapeutic effect, because it did not demonstrate specific therapeutic effects without a placebo control [64]. Further, a sham control is necessary to eliminate any nonspecific physiological effect. Alternatively, comparative effectiveness research might be a good way to assess the effectiveness of acupuncture, because it compares more than two different interventions which have clinical evidence and relevance to clinical settings [65].

Discrepancy in acupoints used in the studies made it difficult to interpret the results and compare the studies. Within 14 studies, approximately 40 body acupoints were used, only LR3, GB34, ST36, and K3 were repeatedly chosen by 5 or 6 studies, while majority of acupoints were used for only in 1 or 2 times. Currently, there was unknown validated treatment protocol of acupuncture for PD, and there was no consensus regarding acupoint selection in the previous studies. Recently, many PD model studies suggest that stimulation at acupoint GB34 and ST36 could enhance motor function and promote dopaminergic cells against toxic insults [31–34]. Studies of fMRI on human subjects found that stimulation on GB34 activated motor-related brain regions such as the putamen, caudate nucleus and thalamus and cerebellum [66]. The efficacy of other acupoints used in the studies was barely investigated. In the future, acupuncture research in PD needs to identify more acupoints that are effective in PD treatment and achieve an agreement on the selection of acupoints in PD acupuncture treatment.

All included studies except one [25] evaluated the patients immediately before and after acupuncture treatment, whereas results of long-term duration of any improvement after acupuncture were not available. Sustainable therapeutic effect is an important part of assessment of effectiveness of any treatment so follow-up evaluation should be conducted in a reasonable time period after completing treatment.

Many methodology flaws were found within included studies. For example, 8 of 14 included studies did not show proper diagnostic criteria for recruitment, and disease severity of the patients eligible to participate the treatment was not disclosed in most studies. Although 7 of 14 studies stated as randomized, only two were single blind controlled and one was double-blind controlled studies. There was a lack of well-design randomized, double-blind, and placebo-controlled studies. Although acupuncture is safe and well-tolerated, majority of studies did not mention the adverse effect and any dropout and withdraw during treatment.

Future clinical acupuncture study should follow accepted standards of methodology such as CONSORT and STRICTA checklists. In particular, studies should have sufficiently large sample sizes, should be based on data from appropriate pilot studies, and to ensure reproducibility. Even if further clinical studies confirm acupuncture to be therapeutic valuable more evidence should be required on whether it has matched the effectiveness of conventional medicine or has significant advantage over conventional medicine. Further, some common practical settings should help improve the quality of future clinical studies. So we propose that (1) comprehensive assessment of patients with PD, not only about motor symptoms also nonmotor symptoms, should be conducted. (2). Using the well-established and universally recognized measures for motor and nonmotor symptoms assessment, such as UPDRS in which the scores of each part should be reported. (3). Acupuncture treatment should include obligatory acupoints and optional acupoints. The former should include proven motor-related acupoints such as GB34 and ST36 for motor symptom treatment [32,66]. The selection of latter is dependent on the nonmotor symptoms and other conditions. (4). Needle duration should be expected to maintain at least 20 min each time for acupuncture to produce a certain level of therapeutic effect. (5). A proper follow-up to evaluate the sustainable therapeutic effect of acupuncture. We hope that this will help reduce the discrepancy between the studies and improve the quality of treatment.

In conclusion, although the evidence for the effectiveness of acupuncture for treating PD is inclusive, data from the reviewed studies showed that therapeutic potential of acupuncture in treating Parkinson's seems rather promising. More studies, either comparative effectiveness research or high-quality placebo-controlled clinical studies should be conducted.

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Conflict of Interest

The authors declare no conflict of interest.

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